

09/486167

PCT/BE98/00124

VANM143.001APC

Date: February 22, 2000

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**TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 USC 371**

International Application No.: PCT/BE98/00124

International Filing Date: August 20, 1998

Priority Date Claimed: August 20, 1997

Title of Invention: PEROXISOME-ASSOCIATED POLYPEPTIDE, NUCLEOTIDE SEQUENCE
ENCODING SAID POLYPEPTIDES AND THEIR USES IN THE DIAGNOSIS AND/OR THE TREATMENT OF
LUNG INJURIES AND DISEASES, AND OF OXIDATIVE STRESS-RELATED DISORDERSApplicant(s) for DO/EO/US: Bernard Knoops, Cedric Hermans, Alfred Bernard, Ruddy Wattiez,
Paul Falmagne

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. (X) This is a **FIRST** submission of items concerning a filing under 35 USC 371.
2. (X) This express request to begin national examination procedures (35 USC 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 USC 371(b) and PCT Articles 22 and 39(1).
3. (X) A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
4. (X) A copy of the International Application as filed (35 USC 371(c)(2))
 - a) () is transmitted herewith (required only if not transmitted by the International Bureau).
 - b) (X) has been transmitted by the International Bureau.
 - c) () is not required, as the application was filed in the United States Receiving Office (RO/US).
5. (X) Amendments to the claims of the International Application under PCT Article 19 (35 USC 371(c)(3))
 - a) () are transmitted herewith (required only if not transmitted by the International Bureau).
 - b) () have been transmitted by the International Bureau.
 - c) () have not been made; however, the time limit for making such amendments has NOT expired.
 - d) (X) have not been made and will not be made.
6. (X) A copy of the International Preliminary Examination Report with any annexes thereto, such as any amendments made under PCT Article 34.
7. (X) An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
8. (X) A FIRST preliminary amendment.
9. (X) International Application as published.
10. (X) PCT Form PCT/IPEA/402.
11. (X) PCT Form PCT/IB/308.

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12. (X) PCT request form.
13. (X) A return prepaid postcard.
14. (X) The following fees are submitted:


				FEES
BASIC FEE				\$840
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total Claims	30 - 20 =	10 ×	\$18	\$180
Independent Claims	1 - 3 =	0 ×	\$78	\$0
Multiple dependent claims(s) (if applicable)			\$260	\$260
TOTAL OF ABOVE CALCULATIONS				\$1280
TOTAL FEES ENCLOSED				\$840

15. (X) The fee for later submission of the signed oath or declaration set forth in 37 CFR 1.492(e) will be paid upon submission of the declaration.
16. (X) A check in the amount of \$840 to cover the above fees is enclosed.
17. (X) The Commissioner is hereby authorized to charge only those additional fees which may be required, now or in the future, to avoid abandonment of the application, or credit any overpayment to Deposit Account No. 11-1410. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

KNOBBE, MARTENS, OLSON & BEAR, LLP
 620 Newport Center Drive
 Sixteenth Floor
 Newport Beach, CA 92660


 Signature

Daniel E. Altman
 Printed Name

34,115
 Registration Number

U.S. Application No.
09/486,167

International Application No.
PCT/BE98/00124

Attorney Docket No.
VANM143.001APC #3

Date: August 4, 2000

Page 1



I hereby certify that this correspondence and all marked attachments are being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on

4-Aug-2000

(Date)

Daniel E. Altman

Daniel E. Altman, Reg. No. 34,115

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 USC 371

International Application No.: PCT/BE98/00124

International Filing Date: August 20, 1998

Priority Date Claimed: August 20, 1997

Title of Invention: PEROXISOME-ASSOCIATED POLYPEPTIDE, NUCLEOTIDE SEQUENCE ENCODING SAID POLYPEPTIDE AND THEIR USES IN THE DIAGNOSIS AND/OR TREATMENT OF LUNG INJURIES AND DISEASES, AND OF OXIDATIVE STRESS-RELATED DISORDERS

Applicant(s) for DO/EO/US: Knoops et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

- (X) This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
 - (X) Copy of Notification of Missing Requirements Under 35 U.S.C. 371 In The United States Designated/Elected Office (DO/EO/US) dated May 4, 2000.
 - (X) An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
 - (X) An extension of time to respond for two month(s) is hereby requested.
- Time Extension Fee:
- (X) two months (\$190 small entity)
- (X) Small Entity Statement.
- (X) A return prepaid postcard.
- (X) The fee of \$65 for submission of the Declaration after 30 months from the priority under 37 C.F.R. 1.492(e).

08/18/2000 ERMANDD 00000139 09486167

01-FC:215 55.00-0P

Date: August 4, 2000

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(X) The fee of \$65 for submission of the Declaration after 30 months from the priority under 37 C.F.R. 1.492(e).

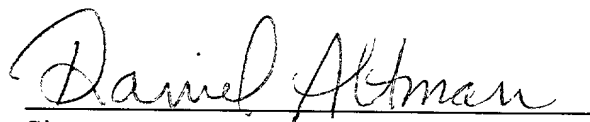
(X) Fees as calculated below:

FILING FEE PAID ON FEBRUARY 22, 2000	\$ 840
FEE FOR EXTENSION OF TIME (LARGE ENTITY) 2 months	\$ 380
SURCHARGE 37 CFR 1.16(e)	\$ + 130
REMAINDER OF FILING FEE TO BE PAID	\$ 440
TOTAL OF ABOVE CALCULATIONS	\$ 1790
REDUCTION BY 1/2 FOR FILING BY SMALL ENTITY. Note 37 CFR 1.9, 1.27, 1.28. If applicable, verified statement must be attached.	\$ - 895
TOTAL OF \$895 SUBTRACT \$840 ALREADY PAID =	\$ 55
TOTAL FEES SUBMITTED HERewith	\$ 55

(X) The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 11-1410. A duplicate copy of this sheet is enclosed.

SEND ALL CORRESPONDENCE TO:

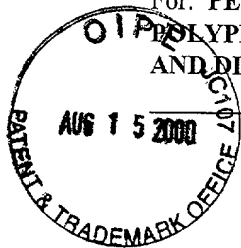
KNOBBE, MARTENS, OLSON & BEAR, LLP
620 Newport Center Drive
Sixteenth Floor
Newport Beach, CA 92660


Signature

Daniel E. Altman
Printed Name

34,115
Registration Number

For: **PEROXISOME-ASSOCIATED POLYPEPTIDE, NUCLEOTIDE SEQUENCE ENCODING SAID
POLYPEPTIDE AND THEIR USES IN THE DIAGNOSIS AND/OR TREATMENT OF LUNG INJURIES
AND DISEASES, AND OF OXIDATIVE STRESS-RELATED DISORDERS**



VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL-ENTITY STATUS

I, the undersigned, do hereby declare that:

☒ I am an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF CONCERN: UNIVERSITE CATHOLIQUE DE LOUVAIN

ADDRESS OF CONCERN: Halles Universitaires, Place de l'Université 1, B-1348 Louvain-La-Neuve, BELGIUM

I further declare that the above-identified small business concern qualifies as a small business concern as defined in 13 CFR 121.12, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees to the United States Patent and Trademark Office, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both. I further declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention described in the patent or application identified above.

The individual, concern or organization identified above has not assigned, granted, conveyed or licensed, and is under no obligation under contract or law to assign, grant, convey or license, any rights in the invention to any person who would not qualify as an independent inventor under 37 CFR 1.9(c) if that person had made the invention, or to any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

If the rights held by the above-identified individual, concern or organization are not exclusive, each individual, concern or organization having rights in the invention are identified below. Each such individual, concern or organization must file separate verified statements averring to their status as small entities.

***NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27).**

FULL NAME: UNIVERSITE DE MONS-HAINAUT

ADDRESS: Place du Parc 20, B-7000 Mons, BELGIUM

☐ INDIVIDUAL ☒ SMALL BUSINESS CONCERN ☐ NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small-entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b)).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Applicants: Knoops et al.
Int'l. Application No.: PCT/BE98/00124

Attorney's Docket No.: VANM143.001APC

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Int'l. Filed: August 20, 1998

For: **PEROXISOME-ASSOCIATED POLYPEPTIDE, NUCLEOTIDE SEQUENCE ENCODING SAID
POLYPEPTIDE AND THEIR USES IN THE DIAGNOSIS AND/OR TREATMENT OF LUNG INJURIES
AND DISEASES, AND OF OXIDATIVE STRESS-RELATED DISORDERS**

NAME OF PERSON SIGNING: *MARCEL CROCHET* MARCEL CROCHET

TITLE OF PERSON (if not an owner or individual): *Rector* Rector

ADDRESS OF PERSON SIGNING: Halles Universitaires, Place de l'Université 1, B-1348 Louvain-La-Neuve,
BELGIUM

SIGNATURE: 

DATE: *31 May 2000*

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022800

VANM143.001APC

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Knoops, et al.) Group Art Unit Unknown
Int'l)
Appl. No. : PCT/BE98/00124)
Int'l Filing)
Date : August 20, 1998)
For : PEROXISOME-ASSOCIATED)
POLYPEPTIDE,)
NUCLEOTIDE SEQUENCE)
ENCODING SAID)
POLYPEPTIDE AND THEIR)
USES IN THE DIAGNOSIS)
AND/OR TREATMENT OF)
LUNG INJURIES AND)
DISEASES, AND OF)
OXIDATIVE STRESS-)
RELATED DISORDERS)
Examiner : Unknown)

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Preliminary to Examination on the merits, please amend the above-captioned patent application as follows:

IN THE SPECIFICATION

On page 1 of the Specification after the Title of the Invention and before the Field of the Invention, on line 13, please insert --This U.S. National Phase application claims priority under 35 U.S.C. §371 of International Application PCT/BE98/00124, filed August 20, 1998, which claims priority of Belgian application BE 9700692, filed August 20, 1997.--.

On page 21, before Claim 1, please cancel the word "CLAIMS" and substitute therefore
--WHAT IS CLAIMED IS:--.

IN THE CLAIMS

1. (Amended) An isolated or purified [Amino acid sequence] polypeptide [having] comprising and amino acid sequence more than 70% [homology with] homologous to [the sequence] SEQ ID [NO 2] NO:2.
2. (Amended) [Amino acid sequence] The isolated or purified polypeptide according to claim 1, [having] more than 85% [homology with the sequence] homologous to SEQ ID [NO 2] NO:2.
3. (Amended) [Amino acid sequence] The isolated or purified polypeptide according to claim 1 [or 2], [having] more than 95% [homology with the] homologous to sequence SEQ ID [NO 2] NO:2.
4. (Amended) [Amino acid sequence] The isolated or purified polypeptide according to [any one of the preceding claims] claim 1, [corresponding to] comprising SEQ ID [NO 2] NO:2 or an immunoreactive portion thereof.
5. (Amended) An isolated or purified polynucleotide [Nucleotide sequence] encoding the amino acid sequence according to [any one of the preceding claims] claim 1 and [presenting] more than 70% [homology with] homologous to SEQ ID [NO 1] NO:1 or its complementary strand.
6. (Amended) An isolated or purified polynucleotide [Nucleotide sequence] according to claim 5, [having] more than 85% [homology with the sequence] homologous to SEQ ID [NO 1] NO:1 or its complementary strand.
7. (Amended) An isolated or purified polynucleotide [Nucleotide sequence] according to claim 5 more than 95% [homology with the sequence] homologous to SEQ ID [NO 1] NO:1 or its complementary strand.
8. (Amended) An isolated or purified polynucleotide [Nucleotide sequence] according to [any one of the claims 5 to 7, corresponding to the sequence] claim 5 comprising SEQ ID [NO 1] NO:1, its complementary strand or a portion thereof specific for SEQ ID [NO 1] NO:1 and comprising more than 15 base pairs.
9. (Amended) A[V]ector comprising the [nucleotide sequence according to any one of the] polynucleotide of claim[s] 5 [to 8].

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Int'l Filing Date : August 20, 1998

10. (Amended) A purified antibody or an active portion of said antibody **[inhibitor directed against]**that specifically binds to the polypeptide **[amino acid or nucleotide sequence according to any one of the]**of claim[s] 1 [to 8].

11. (Amended) **[Inhibitor according to claim 10, being an]**The purified antibody, [preferably] of claim 2 wherein said antibody is a monoclonal antibody[, or a portion of said antibody].

12. (Amended) A **[D]**diagnostic device comprising an element selected from the group consisting of the amino acid sequence [according to any one of the claims 1 to 4]of claim 1, the nucleotide sequence [according to any one of the claims 5 to 8]of claim 2, the [inhibitor according to claim 10 or 11] antibody of claim 10, their portions [or]and a mixture thereof.

13. (Amended) **[Method]**A method for the *in vitro* detection of lung injuries and diseases or oxidative stress-related diseases and disorders, **[especially inflammatory diseases,]**comprising the steps of:

-isolating a sample from a body fluid of a patient, **[preferably a human patient,]**

[-possibly inhibiting the contaminants present in said sample,]

-**[put in]** contacting said sample with an element selected from the group consisting of the amino acid sequence **[according to any one of the claims 1 to 4]of claim 1**, the nucleotide sequence **[according to any one of the claims 5 to 8]of claim 5**, the **[inhibitor according to claim 10 or 11] antibody of claim 10**, their portions **[or]and** a mixture thereof, and

-detecting a reaction of a molecule present in said sample with said element.

14. (Amended) **[Pharmaceutical]**A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an element selected from the group consisting of the amino acid sequence **[according to any one of the claims 1 to 4]of claim 1**, the nucleotide sequence **[according to any one of the claims 5 to 8]of claim 5**, the **[inhibitor according to claim 10 or 11] antibody of claim 10**, their portions **[or]and** a mixture thereof.

15. (Amended) **[Use of the pharmaceutical composition according to claim 14 for the manufacture of a medicament for the prevention and/or the treatment of lung injuries or diseases, and of]**The method of claim 13 wherein said oxidative stress-related diseases or disorders**[, such as]are selected from the group consisting of:** specific cardio-vascular diseases **[like arteriosclerosis,]** neurodegenerative disorders **[such as Alzheimer's disease,**

Int'l Appl. No. : PCT/BE98/00124

Int'l Filing Date : August 20, 1998

Parkinson's disease, amyotrophic lateral sclerosis,] apoptosis and inflammatory reactions, allergic reactions [such as asthma, hay fever and eczema,] high bone mass syndrome, osteopetrosis, osteoporosis-pseudoglioma syndrome, and Bardet-Biedl syndrome 1.

16. (Amended) [Cell]A cell transformed by the vector according to claim 9 or comprising a partial or total genomic deletion of [its]SEQ ID NO:1, or a homologue thereof [nucleotide sequence according to any one of the claims 5 to 8].

17. (Amended) [Non-human]A non-human transgenic animal,[preferably a mammal] transformed by the vector according to claim 9 or comprising a partial or total genomic deletion of [its]SEQ ID NO:1, or a homologue thereof [nucleotide sequence according to any one of the claims 5 to 8].

Please add the following claims:

18. The method of claim 13, wherein said oxidative stress-related diseases and disorders are inflammatory diseases.

19. The method of claim 13, further comprising the step of inhibiting the contaminants present in said sample.

20. The method of claim 13, wherein said patient is a human patient.

21. The method of claim 15 wherein said specific cardio-vascular diseases is arteriosclerosis.

22. The method of claim 15 wherein said neurodegenerative disorders are selected from the group consisting of: Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.

23. The method of claim 15 wherein said allergic reactions are selected from the group consisting of: asthma, hay fever and eczema.

24. The transgenic animal of claim 16, wherein said animal is a mammal.

REMARKS

Claims 1-17 have been amended to conform to U.S. practice before the USPTO. Claims 18-24 have been added. Support for added Claims 18-24 can be found in the claims as filed. The Specification has been amended to include the priority international document and to correct minor informalities. No new matter has been added herewith. As a result of the amendments, Claim 1-24 are pending.

Int'l Appl. No. : PCT/BE98/00124
Int'l Filing Date : August 20, 1998

This Preliminary Amendment enters a Sequence listing, pages 1-13. Enclosed herewith are: (1) a paper copy of the Sequence Listing, (2) and a computer readable version of the Sequence Listing. In view of the foregoing, the application is believed to fully comply with the Sequence Listing disclosure requirements.

VERIFICATIONS UNDER 37 C.F.R. §1.821(f) & (g)

All of the sequences in the attached Sequence Listing were included in the application as filed. Pursuant to 37 C.F.R. § 1.821(g), no new matter is being added herewith. As required under 37 C.F.R. § 1.821(f), I hereby verify that the data on the computer readable disk and the paper copies of the Sequence Listing submitted herewith are identical.

Conclusion

Should there be any questions concerning this application, the Examiner is invited to contact the undersigned attorney at the telephone number appearing below.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated:

22 Feb. 2000

By:

Daniel Altman

Daniel E. Altman
Registration No. 34,115
Attorney of Record
620 Newport Center Drive
Sixteenth Floor
Newport Beach, CA 92660
(949) 760-0404

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012500

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:

(A) NAME: UNIVERSITE CATHOLIQUE DE LOUVAIN
Halles Universitaires
(B) STREET: Place de l' Universite, 1
(C) CITY: LOUVAIN-LA-NEUVE
(E) COUNTRY: BELGIUM
(F) POSTAL CODE (ZIP): B-1348

(A) NAME: UNIVERSITE DE MONS-HAINAUT
(B) STREET: Place du Parc 20
(C) CITY: MONS
(E) COUNTRY: BELGIUM
(F) POSTAL CODE (ZIP): B-7000

(ii) TITLE OF INVENTION: PEROXISOME-ASSOCIATED PEPTIDE, NUCLEOTIDE
SEQUENCE ENCODING SAID PEPTIDE AND THEIR USES IN THE
DIAGNOSTIC AND/OR THE TREATMENT OF LUNG INJURIES AND
DISEASES, AND OF OXIDATIVE STRESS-RELATED DISORDERS

(iii) NUMBER OF SEQUENCES: 19

(iv) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPO)

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 805 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 193..681

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

GCCAGGAGGC GGAGTGAAG TGGCCGTGGG GCGGGTATGG GACTAGCTGG CGTGTGCGCC 60
CTGAGACGCT CAGCGGGCTA TATACTCGTC GGTGGGGCCG GCGGTCAGTC TCGGCAGCG 120

GCAGCAAGAC GGTGCAGTGA AGGAGAGTGG GCGTCTGGCG GGGTCCGCAG TTTCAGCAGA	180
GCCGCTGCAG CC ATG GCC CCA ATC AAG GTG GGA GAT GCC ATC CCA GCA Met Ala Pro Ile Lys Val Gly Asp Ala Ile Pro Ala 1 5 10	228
GTG GAG GTG TTT GAA GGG GAG CCA GGG AAC AAG GTG AAC CTG GCA GAG Val Glu Val Phe Glu Gly Glu Pro Gly Asn Lys Val Asn Leu Ala Glu 15 20 25	276
CTG TTC AAG GGC AAG AAG GGT GTG CTG TTT GGA GTT CCT GGG GCC TTC Leu Phe Lys Gly Lys Lys Gly Val Leu Phe Gly Val Pro Gly Ala Phe 30 35 40	324
ACC CCT GGA TGT TCC AAG ACA CAC CTG CCA GGG TTT GTG GAG CAG GCT Thr Pro Gly Cys Ser Lys Thr His Leu Pro Gly Phe Val Glu Gln Ala 45 50 55 60	372
GAG GCT CTG AAG GCC AAG GGA GTC CAG GTG GTG GCC TGT CTG AGT GTT Glu Ala Leu Lys Ala Lys Gly Val Gln Val Val Ala Cys Leu Ser Val 65 70 75	420
AAT GAT GCC TTT GTG ACT GGC GAG TGG GGC CGA GCC CAC AAG GCG GAA Asn Asp Ala Phe Val Thr Gly Glu Trp Gly Arg Ala His Lys Ala Glu 80 85 90	468
GGC AAG GTT CGG CTC CTG GCT GAT CCC ACT GGG GCC TTT GGG AAG GAG Gly Lys Val Arg Leu Leu Ala Asp Pro Thr Gly Ala Phe Gly Lys Glu 95 100 105	516
ACA GAC TTA TTA CTA GAT GAT TCG CTG GTG TCC ATC TTT GGG AAT CGA Thr Asp Leu Leu Leu Asp Asp Ser Leu Val Ser Ile Phe Gly Asn Arg 110 115 120	564
CGT CTC AAG AGG TTC TCC ATG GTG GTA CAG GAT GGC ATA GTG AAG GCC Arg Leu Lys Arg Phe Ser Met Val Val Gln Asp Gly Ile Val Lys Ala 125 130 135 140	612
CTG AAT GTG GAA CCA GAT GGC ACA GGC CTC ACC TGC AGC CTG GCA CCC Leu Asn Val Glu Pro Asp Gly Thr Gly Leu Thr Cys Ser Leu Ala Pro 145 150 155	660
AAT ATC ATC TCA CAG CTC TGA GGCCCTGGGC CAGATTACTT CCTCCACCCC Asn Ile Ile Ser Gln Leu * 160	711
TCCCTATCTC ACCTGCCCAG CCCTGTGCTG GGGCCCTGCA ATTGGAATGT TGGCCAGATT	771
TCTGCAATAA ACACTTGTGG TTTGCGGAAA AAAA	805

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 163 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

AGTGCCGCGG TGACTATGGC CCCGATCAAG GTGGGAGACA CCATTCCCTC AGTGGAGGTA	180
TTTGRAGGGG AACCTGGAAA GAAGGTGAAC TTGGCAGAGC TGTTCAAGGA CAAGAAAGGT	240
GTTTTGTTTG GAGTCCCTGG GGCATTTACA CCTGGCTGTT CCAAGACCCA TCTGCCTGGG	300
TTTGTGGAGC AAGCCGGAGC TCGAAGGCC AAGGGAGCAC AAGTGGTGGC CTGTCTGAGT	360
GTTAATGATG YCTTCGTGAC TGCAGAGTGG GGTCGAGCCC ACCAGGCAGA AGGCAAGGTT	420
CAGCTCCTGG CTGACCCAC TGGAGCTTTT GGAAAGGAGA CAGATTTACT ACTAGATGAT	480
TCTTTGGTGT CTCTCTTTGG GAATCGTCGG CTAAAAAGGT TCTCCATGGT GATAGACAAG	540
GGCGTAGTAA AGGCACTGAA CGTGGAGCCG GATGGCACAG GCCTCACCTG CAGCCTGGCC	600
CCCAACATCC TCTCACAAC CTGAGGCCCT GACCAGAATG TCCTCTGACT CTCCCATCTC	660
CTCCACCCAG CTCTGGGCCA AAGGCCCAGT ACCTCCTTAC CTGAGGGCCA CTGGAATGGA	720
ACCTTGACAA TATTTCTGCA ATAAACAGTT TAATTTGTGA AAAAAAAAAA AAAAAAAAAA	780

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 162 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Rattus Rattus

(ix) FEATURE:

- (A) NAME/KEY: Modified-site
- (B) LOCATION:17
- (D) OTHER INFORMATION:/product= "Glu or Gly"

(ix) FEATURE:

- (A) NAME/KEY: Modified-site
- (B) LOCATION:63
- (D) OTHER INFORMATION:/product= "Leu or Pro"

(ix) FEATURE:

- (A) NAME/KEY: Modified-site
- (B) LOCATION:79
- (D) OTHER INFORMATION:/product= "Ala or Val"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Met	Ala	Pro	Ile	Lys	Val	Gly	Asp	Thr	Ile	Pro	Ser	Val	Glu	Val	Phe
1				5					10					15	

Xaa Gly Glu Pro Gly Lys Lys Val Asn Leu Ala Glu Leu Phe Lys Asp
 20 25 30
 Lys Lys Gly Val Leu Phe Gly Val Pro Gly Ala Phe Thr Pro Gly Cys
 35 40 45
 Ser Lys Thr His Leu Pro Gly Phe Val Glu Gln Ala Gly Ala Xaa Lys
 50 55 60
 Ala Lys Gly Ala Gln Val Val Ala Cys Leu Ser Val Asn Asp Xaa Phe
 65 70 75 80
 Val Thr Ala Glu Trp Gly Arg Ala His Gln Ala Glu Gly Lys Val Gln
 85 90 95
 Leu Leu Ala Asp Pro Thr Gly Ala Phe Gly Lys Glu Thr Asp Leu Leu
 100 105 110
 Leu Asp Asp Ser Leu Val Ser Leu Phe Gly Asn Arg Arg Leu Lys Arg
 115 120 125
 Phe Ser Met Val Ile Asp Lys Gly Val Val Lys Ala Leu Asn Val Glu
 130 135 140
 Pro Asp Gly Thr Gly Leu Thr Cys Ser Leu Ala Pro Asn Ile Leu Ser
 145 150 155 160
 Gln Leu

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 675 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Mouse

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 99..588

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

TGCTCCGTGC ATCGACGTGC TTGGCAGGCA GAGCAGGCCG GAAAGAAGCA GGTGTTGGGAGT	60
GTGGCGGAGC CCGCAGCTTC AGCAGCTCCG CGGTGACCAT GGCCCCGATC AAGGTGGGAG	120
ATGCCATTCC CTCAGTGGAG GTATTTGAAG GGGAACCGGG AAAGAAGGTG AACTTGGCAG	180
AGCTGTTCAA GGGCAAGAAA GGTGTTTTGT TTGGAGTCCC TGGGGCATTT ACACCTGGCT	240

GTTCTAAGAC CCACCTGCCT GGGTTTGTGG AGCAAGCTGG AGCTCTGAAG GCTAAGGGAG 300
 CGCAGGTGGT GGCCTGTCTG AGCGTTAATG ACGTCTTTGT GATTGAAGAG TGGGGTCGAG 360
 CCCACCAGGC AGAAGGCAAG GTTCGGCTCC TGGCTGACCC CACTGGAGCC TTTGGGAAGG 420
 CGACAGACTT ATTATTGGAT GATTCTTTGG TGTCTCTCTT TGGGAATCGT CGGCTGAAAA 480
 GGTCTCCAT GGTGATAGAC AACGGCATAG TGAAGGCACT GAACGTGGAG CCAGATGGCA 540
 CAGGCCTCAC CTGCAGCCTG GCCCCAACA TCCTCTCCA ACTCTGAGGC CCTGGCCAGA 600
 TGTCTCTGA CTCTCCCATC TCTCCCACCC GGCTCTAGGC CAAAAGGCTC GGTACCTCCT 660
 TACTGGGAGC CACGT 675

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 162 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Mouse

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

Met	Ala	Pro	Ile	Lys	Val	Gly	Asp	Ala	Ile	Pro	Ser	Val	Glu	Val	Phe
1				5					10					15	
Glu	Gly	Glu	Pro	Gly	Lys	Lys	Val	Asn	Leu	Ala	Glu	Leu	Phe	Lys	Gly
			20					25					30		
Lys	Lys	Gly	Val	Leu	Phe	Gly	Val	Pro	Gly	Ala	Phe	Thr	Pro	Gly	Cys
			35				40					45			
Ser	Lys	Thr	His	Leu	Pro	Gly	Phe	Val	Glu	Gln	Ala	Gly	Ala	Leu	Lys
			50				55				60				
Ala	Lys	Gly	Ala	Gln	Val	Val	Ala	Cys	Leu	Ser	Val	Asn	Asp	Val	Phe
			65			70				75				80	
Val	Ile	Glu	Glu	Trp	Gly	Arg	Ala	His	Gln	Ala	Glu	Gly	Lys	Val	Arg
				85				90						95	
Leu	Leu	Ala	Asp	Pro	Thr	Gly	Ala	Phe	Gly	Lys	Ala	Thr	Asp	Leu	Leu
			100					105					110		
Leu	Asp	Asp	Ser	Leu	Val	Ser	Leu	Phe	Gly	Asn	Arg	Arg	Leu	Lys	Arg
			115				120						125		

Phe Ser Met Val Ile Asp Asn Gly Ile Val Lys Ala Leu Asn Val Glu
 130 135 140

Pro Asp Gly Thr Gly Leu Thr Cys Ser Leu Ala Pro Asn Ile Leu Ser
 145 150 155 160

Gln Leu

(2) INFORMATION FOR SEQ ID NO: 7:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 469 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Homo sapiens

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 161..382

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

GGGTATGGGA CTAGCTGGCG TGTGCGCCCT GAGACGCTCA GCGGGCTATA TACTCGTCGG	60
TGGGGCCGGC GGTCAGTCTG CGGCAGCGGC AGCAAGACGG TGCAGTGAAG GAGAGTGGGC	120
GTCTGGCGGG GTCCGCAGTT TCAGCAGAGC CGCTGCAGCC ATGGCCCCAA TCAAGGTTTC	180
GCTCCTGGCT GATCCCACTG GGGCCTTTGG GAAGGAGACA GACTTATTAC TAGATGATTC	240
GCTGGTGTCC ATCTTTGGGA ATCGACGTCT CAAGAGGTTT TCCATGGTGG TACAGGATGG	300
CATAGTGAAG GCCCTGAATG TGGAACCAGA TGGCACAGGC CTCACCTGCA GCCTGGCACC	360
CAATATCATC TCACAGCTCT GAGGCCCTGG GCCAGATTAC TTCCTCCACC CCTCCCTATC	420
TCACCTGCCC AGCCGTGTGC TGGGGCCCTG CAATTGGAAT GTTGGCCAG	469

(2) INFORMATION FOR SEQ ID NO: 8:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 601 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION:161..514

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

GGGTATGGGA CTAGCTGGCG TGTGCGCCCT GAGACGCTCA GCGGGCTATA TACTCGTCGG 60
TGGGGCCGGC GGTCAGTCTG CGGCAGCGGC AGCAAGACGG TGCAGTGAAG GAGAGTGGGC 120
GTCTGGCGGG GTCCGCAGTT TCAGCAGAGC CGCTGCAGCC ATGGCCCCAA TCAAGACACA 180
CCTGCCAGGG TTTGTGGAGC AGGCTGAGGC TCTGAAGGCC AAGGGAGTCC AGGTGGTGGC 240
CTGTCTGAGT GTTAATGATG CCTTTGTGAC TGGCGAGTGG GGCCGAGCCC ACAAGGCGGA 300
AGGCAAGGTT CGGCTCCTGG CTGATCCAC TGGGGCCTTT GGAAGGAGA CAGACTTATT 360
ACTAGATGAT TCGCTGGTGT CCATCTTTGG GAATCGACGT CTCAAGAGGT TCTCCATGGT 420
GGTACAGGAT GGCATAGTGA AGGCCCTGAA TGTGGAACCA GATGGCACAG GCCTCACCTG 480
CAGCCTGGCA CCCAATATCA TCTCACAGCT CTGAGGCCCT GGGCCAGATT ACTTCCTCCA 540
CCCCCTCCCTA TCTCACCTGC CCAGCCCTGT GCTGGGGCCC TGCAATTGGA ATGTTGGCCA 600
G 601

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 604 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION:161..517

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

GGGTATGGGA CTAGCTGGCG TGTGCGCCCT GAGACGCTCA GCGGGCTATA TACTCGTCGG 60

TGGGGCCGGC GGTCACTCTG CGGCAGCGGC AGCAAGACGG TGCAGTGAAG GAGAGTGGGC	120
GTCTGGCGGG GTCCGCAGTT TCAGCAGAGC CGCTGCAGCC ATGGCCCCAA TCAAGGTGGG	180
AGATGCCATC CCAGCAGTGG AGGTGTTTGA AGGGGAGCCA GGGAACAAGG TGAACCTGGC	240
AGAGCTGTTC AAGGGCAAGA AGGGTGTGCT GTTTGGAGTT CCTGGGGCCT TCACCCCTGG	300
ATGTTCCAAG GTTCGGCTCC TGGCTGATCC CACTGGGGCC TTTGGGAAGG AGACAGACTT	360
ATTACTAGAT GATTCGCTGG TGTCCATCTT TGGGAATCGA CGTCTCAAGA GGTTCTCCAT	420
GGTGGTACAG GATGGCATAG TGAAGGCCCT GAATGTGGAA CCAGATGGCA CAGGCCTCAC	480
CTGCAGCCTG GCACCCAATA TCATCTCACA GCTCTGAGGC CCTGGGCCAG ATTACTTCCT	540
CCACCCCTCC CTATCTCACC TGCCCAGCCC TGTGCTGGGG CCCTGCAATT GGAATGTTGG	600
CCAG	604

(2) INFORMATION FOR SEQ ID NO: 10:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 2710 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Homo sapiens

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:2516..2710

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:2074..2135

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:1932..1970

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:1728..1859

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:802..936

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

TCTGTCCCTT	AGCGCCCCCG	CGGGGGCTTA	CCCCATCCCA	CTCCATGACC	TCCCCTCCCC	60
CCATGGCGAA	TTCCCACCTT	TCTGTCTTTC	ACTCACTTCC	TGGAACCGTC	CCCAGGGCCT	120
TGGACCTTCC	CCCTTCTCCT	CCCAAACCTT	GTGAGACCCC	ATTCCCTTTC	TACTTCATCC	180
TGCTCTCAAC	TTTTGGGCTC	CTCAGAGGCC	CTCACCCCTG	ACTCTCTCTC	CCTACCCACT	240
CTGGTCCCAT	GAAGCCCTCA	AGTACTCTGG	GGATGGATCC	TTCCCCCTTC	AAAAGATTCC	300
TTCTTTTGTT	CTACACCTCC	TGGGTGTAGG	GGCCTGGACA	CCCTCCCCCA	ACGTTCCACC	360
TGCCGCTGCC	CTTCCTCTTC	CTCCTCCTGA	GGGTGGGACC	CTCAGACCTG	GCCAAGATCC	420
TCTCCCTCCA	TGTTGTCAGG	GACTCCTCCT	CACCCCCAAA	TACAGCCCTC	TAGCCCCTGT	480
CCATTTTATT	CCACTCCTTT	CCTGTAACCT	AGACAGCATG	TTATGCAACC	CTTTGCGACA	540
CATGGGGAAA	CCTTCCCTCC	CTTCCTCTGT	TGTCACCAAT	GGCCCCTTAA	GAGGAGCAGG	600
GCCACCTTGA	AACTTGAGG	ATATGGGGTA	ACCCAGTGGG	AGCGGGCAGG	GAGGGCCCTT	660
GGAAACTGAC	AGGGCTGGAG	TATCCTGCTG	GGTTTCAGCC	CCGGTTCCTG	CAGGCACAGC	720
TGCCAGGCTC	TCTGTTACAC	TTCCTGCCTC	TGGTTTGCCC	CGGCTCCCTC	ACCCCCCTTA	780
CCCTGGAGTC	CTTCCTTCTA	GGTGGGAGAT	GCCATCCCAG	CAGTGGAGGT	GTTTGAAGGG	840
GAGCCAGGGA	ACAAGGTGAA	CCTGGCAGAG	CTGTTCAAGG	GCAAGAAGGG	TGTGCTGTTT	900
GGAGTTCCTG	GGGCCTTCAC	CCCTGGATGT	TCCAAGGTGA	GGCCCTTCCC	CTTCTGAAGA	960
TCAGGACCTG	GGGATCTTTT	GTGTTGCTCT	TAAGTCCTCC	ACATAGTCCT	GATAGGACTC	1020
CTAAAAAGCA	TTTCAGTGCC	ATCACAAAAC	AAGTAGAGCT	GGGTAGAGCT	GGGCGCGGTG	1080
GCTCACGCCT	GTAATCCCAG	CACTTTGGA	GGCCAAGGCG	GGTGGATCAC	GAGGTCAGGA	1140
GTCCAAAACC	AGCCTGGCCA	AGATGGTGAA	ACCCTGTCTC	TACTAAAAAT	GCAAAAAAAT	1200
CAGCCGGATA	TGGTGGCGGG	CGCCTGTAAT	CCCAGGTATT	GGGGAGGCTG	AGGCAGAGAA	1260
TTGCTTGAAC	CCAGGAGGCG	TAGGTTGCAG	TGAGTGGAGA	TCGTGCCTCT	GCAGTCCAGC	1320
CTGGGTGAAA	GAGCGAGACT	CCGTCTCAA	ATGAAAAAAA	AAAAAGAAAA	CAAGTAGAGA	1380
CTGCAAAAAG	GGAACAGTAC	CGGGAATGTT	GGAGAAAAAC	ATACTACAAT	TAAATCCAAC	1440
ACCCCTGTTG	GTCCTGCTAA	ATGACAGGCA	CTGTGGAAGG	TGCTTGGGAC	TCAGATAAAT	1500
AAGACAAAGA	TCTGCCCATG	GAAAGTTCAC	GTCTGGACCA	TAAGGCATTA	GGTTTCATTC	1560
TGAGCTTCCT	AGTGGCCAAG	GCAAAAAGGA	AATAGAATGG	TTTAGACAGC	TCTCATTGTC	1620
TGATCAAAGG	TGTTGAGGCA	GAGCACTGAG	GAGGGCCTGG	AGATAAAGGG	TGGGCTGGGG	1680
GTCAGATGCA	GTTATCCCTT	TGCCGACCCT	TTGTTCCCCT	TCCTCAGACA	CACCTGCCAG	1740
GGTTTGTGGA	GCAGGCTGAG	GCTCTGAAGG	CCAAGGGAGT	CCAGGTGGTG	GCCTGTCTGA	1800
GTGTTAATGA	TGCCTTTGTG	ACTGGCGAGT	GGGGCCGAGC	CCACAAGGCG	GAAGGCAAGG	1860

TGAGGTGAGG GGCCTGCAGG GAGTCAGGAC CAGGTAGGAT ATTCTTCTTG TGACCTCTAC	1920
TTTCTCTGCA GGTTCGGCTC CTGGCTGATC CCACTGGGGC CTTTGGGAAG GTGAGTGTTT	1980
CCCTGACCGC CACAGGGACA TGGCGGTGCG GGGAGCAGTG GGGGCCCTTG GCCTCTTCAA	2040
GGATTTCTGA CACTTTTCTC TGTCTCTTCT TAGGAGACAG ACTTATTACT AGATGATTCG	2100
CTGGTGTCCA TCTTTGGGAA TCGACGTCTC AAGAGGTAAA AGTGGAGAGT CCTCTGTGGA	2160
GAAAGTCCTC TGTGGGAGAG AGTCCTCTGT GGGAGAGAGT CCTCTGTGGA GAGGGTCCTC	2220
TGTGGGAAGA GTCGTCTGTG GGGGAGATGT GTGGGAGAGA GTCCTGTGTG GGGAGAGTCT	2280
TCTGTAGGGG AGAGTCCTCT GGGGAGAGAG TCCTGTGTGG GGGAGAGTCC TCTGTGGGGA	2340
GAGTCCTCTG TGTGGAGAGA GTCCTGTGTG GTGGTGAGTC CTCTGTGGGG GAGAGTCCTC	2400
TGTGGGGGGA GTCCTCTCTG GAGTTCTCTT GGGCCCCTGG CTGTTCCTG CCTGTCTCCA	2460
TGCCCAGCCT CCAAGCCCAG GCTGATGCAG CTGGCTGGGC CCCTCTTTCC GGCAGGTTCT	2520
CCATGGTGGT ACAGGATGGC ATAGTGAAGG CCCTGAATGT GGAACCAGAT GGCACAGGCC	2580
TCACCTGCAG CCTGGCACCC AATATCATCT CACAGCTCTG AGGCCCTGGG CCAGATTACT	2640
TCCTCCACCC CTCCCTATCT CACCTGCCCA GCCCTGTGCT GGGGCCCTGC AATTGGAATG	2700
TTGGCCAGAT	2710

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 25 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

GCCATCCCAG CAGTGGAGGT GTTTG

25

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

TTGAACAGCT CTGCCAGGTT CACC

24

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

TGGAGGTGTT TGAAGGGGAG CCAG

24

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

CAGGTTACCC TTGTTCCCTG GCTC

24

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

GGGTATGGGA CTAGCTGGCG

20

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

CTGGCCAACA TTCCAATTGC AG

22

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

ATGTTATGCA ACCCTTTGCG ACAC

24

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

GTGTTTGAAG GGGAGCCAGG GAAC

24

(2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

AGAGACAGGG TTTCACCATC TTGG

24

5

PEROXISOME-ASSOCIATED POLYPEPTIDE, NUCLEOTIDE SEQUENCE
10 ENCODING SAID POLYPEPTIDE AND THEIR USES IN THE DIAGNOSIS
AND/OR THE TREATMENT OF LUNG INJURIES AND DISEASES, AND OF
OXIDATIVE STRESS-RELATED DISORDERS

Field of the invention

15 The present invention is related to a new peroxisome-associated polypeptide, the nucleotide sequence encoding said polypeptide and portions thereof as well as their uses in the diagnosis of several diseases, especially the diagnosis and/or the treatment of lung injuries and
20 diseases, and of oxidative stress-related disorders.

Background of the invention

The peroxisomes are organelles nearly ubiquitous in eukaryotic cells. They contain enzymes
25 essential for various catabolic and anabolic pathways. Some of these enzymes are expressed constitutively while others can be induced under appropriate conditions. Peroxisomes carry out a variety of essential reactions such as peroxisomal oxidation and respiration, fatty acid beta-
30 oxidation, cholesterol and dolichol metabolism, ether-phospholipid synthesis, and glyoxylate and pipecolic acid metabolism.

The peroxisomal respiratory pathway is based upon the formation of hydrogen peroxide by a collection of oxidases and the decomposition of the H_2O_2 by catalase. These reactions are responsible for 20% of oxygen
5 consumption in liver, and several oxidases have been identified in peroxisomes. Ethanol elimination via catalase in peroxisomes may be significant in addition to the oxidation via cytosolic alcohol dehydrogenase.

The peroxisomal beta-oxidation system
10 catalyses the beta-oxidative chain shortening of a specific set of compounds which can not be handled by mitochondria : very long chain fatty acids, di- and trihydroxycholestanoic acids, pristanic acid, long chain dicarboxylic acids, several prostaglandins, several leukotrienes, 12- and 15-
15 hydroxyeicosatetraeonic acid, and several mono- and polyunsaturated fatty acids, which are of direct diagnostic relevance for some peroxisomal disorders.

Peroxisomes play also a major role in the synthesis of cholesterol and other isoprenoids. Fibroblasts
20 from patients affected by disorders of peroxisome biogenesis show low capacity to synthesise cholesterol.

Two enzyme activities responsible for introduction of the characteristic ether linkage in ether-linked phospholipids (dihydroacetonephosphate
25 acyltransferase (DHAPAT) and alkyl dihydroxyacetonephosphate synthase (alkyl-DHAP synthase)) are localised in peroxisomes. These enzymes are not yet cloned. As demonstrated by the identification of patients with deficiency of either DHAPAT or alkyl-DHAP synthase with
30 severe clinical abnormalities, ether-phospholipids are of major importance in humans.

Peroxisomes are able to detoxify glyoxylate via alanine/glyoxylate aminotransferase. The deficiency of this cloned enzyme causes hyperoxaluria type I.

L-pipecolate is a minor metabolite of L-lysine and is
5 catabolised by the L-pipecolate oxidase localised in peroxisomes. The enzyme is deficient in cerebro-hepato-renal (Zellweger) syndrome.

In human, the importance of peroxisomes was emphasised by a number of inherited diseases involving
10 either a defect in the biogenesis of peroxisomes or a deficiency of one (or more) peroxisomal enzymes. So far, 12 different peroxisomal disorders have been described and most of them are lethal.

A wide variety of chemicals have been showed
15 to produce peroxisome proliferation and induction of peroxisomal and microsomal fatty acids-oxidising enzymes activities in rats and mice. Several peroxisomes proliferators have been shown to increase the incidence of liver tumours in these species. Proposed mechanisms of
20 liver tumour formation by peroxisomes proliferators include induction of sustained oxidative stress.

Therefore, newly identified molecules associated with peroxisomes could be used for the development of diagnostic tools and possibly for the
25 improvement of several therapeutical applications of various diseases associated with peroxisomal disorders. In addition, it is useful to identify the molecules present in specific organs like the lung and which may be used as specific markers of inflammatory diseases as well as lung
30 injuries or diseases.

Summary of the invention

The Inventors have isolated and purified a new sequence of a low molecular weight human broncho-alveolar polypeptide. Said mammal, preferably human, protein or polypeptide (hereafter identified as B18hum
5 protein) has been sequenced and its corresponding genomic DNA (SEQ ID NO 8) and cDNA (SEQ ID NO 1) have been identified. Similarly, the corresponding nucleotide and amino acid sequence from a rat (SEQ ID NO 3 and 4) and from
10 a mouse (SEQ ID NO 5 and 6) have been obtained.

Said sequences present several homologies with other peroxisomal proteins of yeast and comprise a carboxy-terminal tripeptide SQL which is necessary for the specific targeting and translocation of several proteins
15 into the peroxisome.

Therefore, the present invention is related to a new isolated and purified polypeptide sequence having a amino acid sequence which presents more than 70% homology, advantageously more than 85% homology, more
20 preferably more than 95% homology, with the amino acid sequence SEQ ID NO 2., Said amino acid sequence is advantageously obtained from a mammal, preferably from a rat, a mouse or a human.

The present invention is also related to the
25 isolated and purified polypeptide sequence corresponding to the amino acid sequence SEQ ID NO 2 or a portion thereof, preferably an immunoreactive portion (putative immunogenic domain or T or B cell epitopes).

Said portions are advantageously comprised
30 between :

- Glutamic acid position 13 - Glutamic acid position 27
- Alanine position 26 - Leucine position 36

- Alanine position 42 - Glutamic acid position 57
- Glutamic acid position 57 - Valine position 69
- Valine position 80 - Leucine position 97
- Arginine position 95 - Leucine position 112
- 5 - Serine position 118 - Serine position 129
- Valine position 137 - Threonine position 150

Preferably, said portion has more than 10, 20, 30, 50 or 70 amino acids. Specific portions of the amino acid sequence SEQ ID NO 2 are also portions of more
10 than 70 amino acids which present at least 80% of the proteinic activity (see example 5) of the complete SEQ ID NO 2 sequence. Therefore, the amino acid sequence according to the invention can be partially deleted while maintaining its activity, preferably its anti-oxidative activity, which
15 will be described hereafter.

According to the invention, the amino acid sequence SEQ ID NO 2 presents a pI of 7.16 and a molecular weight of 17047 Dalton as hereafter defined by bidimensional electrophoresis.

20 The present invention is also related to the nucleotide sequence encoding the amino acid sequence according to the invention and its regulatory sequences upstream said coding sequence. A nucleotide sequence encoding the polypeptide according to the invention is a
25 genomic DNA (see SEQ ID NO 10), a cDNA (see SEQ ID NO 1) or a mRNA, possibly comprising said upstream regulatory sequence. Advantageously, said nucleotide sequence presents more than 70%, advantageously more than 85%, more preferably more than 95% homology with SEQ ID NO 1 or its
30 complementary strand.

According to a preferred embodiment of the present invention, said nucleotide sequence corresponds to the nucleotide sequence SEQ ID NO 1, its complementary strand or a portion thereof.

5 "A portion of the nucleotide sequence SEQ ID NO 1" means any nucleotide sequence of more than 15 base pairs (such as a primer, a probe or an antisense nucleotide sequence) which allow the specific identification, reconstitution or blocking of the complete nucleotide
10 sequence SEQ ID NO 1 (including its regulatory sequences upstream the coding sequence).

Said portions allow the specific identification, reconstitution or blocking by specific hybridisation with the nucleotidic sequence SEQ ID NO 1,
15 preferably under standard stringent conditions, with sequences like probes or primers possibly labelled with a compound (radioactive compound, enzyme, fluorescent marker, etc.), and can be used in a specific diagnostic or dosage method like probe hybridisation (see Sambrook et al., §§
20 9.47-9.51 in *Molecular Cloning : A Laboratory Manual*, Cold Spring Harbor, Laboratory Press, Cold Spring Harbor, New York (1989)), genetic amplification (like PCR (US patent 4,683,195), LCR (Wu et al., *Genomics* 4, pp. 560-569), CPR (US patent 5,011,769)).

25 Exemplary stringent hybridisation conditions are as follows : hybridisation at 42 °C in 50% formamide 5x SSC, 20 mM sodium phosphate, pH 6.8 washing in 0.2x SSC at 55 °C. It is understood by those skilled in the art that variation of these conditions occur based on the length and
30 GC nucleotide content of the sequence to be hybridised. Formulas standard in the art are appropriated for

determining exact hybridisation conditions (see Sambrook et al.

Preferred examples of said nucleotide portions are as follows :

	<u>Sequence</u>	<u>Position</u>
5	5'-gccatcccagcagtgagggtgtttg-3'	(SEQ ID NO 11) 217-241
	5'-ttgaacagctctgccagggttcacc-3'	(SEQ ID NO 12) 261-284
	5'-tggaggtgtttgaaggggagccag-3'	(SEQ ID NO 13) 230-253
	5'-caggttcaccttgttcctggctc-3'	(SEQ ID NO 14) 247-270
10	5'-gggtatgggactagctggcg-3'	(SEQ ID NO 15) 33-52
	5'-ctggccaacattccaattgcag-3'	(SEQ ID NO 16) 747-768
	and the sequences of respectively 601 (SEQ ID NO 8), 604 (SEQ ID NO 9) and 469 (SEQ ID NO 7) base pairs corresponding to specific mRNA alternative splicing of the	
15	B18 human nucleotide sequence as described in Figure 4 (the known genomic sequence incorporating several introns and exons is represented in the sequence SEQ ID NO 10).	

Said sequences may be used for a genetic amplification or a probe hybridisation as above-described.

- 20 The present invention is also related to a vector comprising the necessary elements for the injection, transfection or transduction of cells and having incorporated one or more of the nucleotide sequences according to the invention. The vector according to the
- 25 invention is selected from the group consisting of viruses, plasmids, phagemides, cationic vesicles, liposomes or a mixture thereof. Said vector may comprise also one or more adjacent regulatory sequences (such as promoter(s), secretion and termination signal sequence(s)),
- 30 advantageously operably linked to the nucleotide sequence according to the invention.

The present invention is also related to the cell transformed by said vector and expressing the polypeptide according to the invention.

The nucleotide sequence according to the invention can be also introduced in said cell by the formation of CaPO_4 -nucleic acid precipitate, DEAE-dextran-nucleic acid complex or by electroporation.

Another aspect of the present invention is related to an inhibitor of the polypeptide according to the invention or the nucleotide sequence according to the invention (including the upstream sequences like promoter-operator regulatory sequence which may be inhibited by a cis- and/or transactivating repressor). Said inhibitor is advantageously an antibody or a fragment of said antibody such as an hypervariable portion of said antibody directed against the amino acid or nucleotide sequence of the polypeptide according to the invention. Other examples of inhibitors according to the invention are antisense nucleotide sequences which allow the blocking of the expression of the nucleotide sequence according to the invention.

Another aspect of the present invention is related to a diagnostic device (such as a diagnostic kit or a chromatographic column) comprising an element selected from the group consisting of the amino acid sequence of said polypeptide, its nucleotide sequence, and/or the inhibitor according to the invention or a fragment thereof as above-described. Said diagnostic device may comprise also necessary reactants and media for the diagnostic and/or dosage of the nucleotide and/or amino acid sequence of the polypeptide according to the invention, which are based upon the method selected from the group consisting of

in situ hybridisation, hybridisation by labelled antibodies, especially RIA (Radio Immuno Assay) or ELISA (Enzymes Linked Immuno-Sorbent Assay) technologies, detection upon filter, upon solid support, in solution, in sandwich, upon gel, dot blot hybridisation, Northern blot hybridisation, Southern blot hybridisation, isotopic or non-isotopic labelling (by immunofluorescence or biotinilised probes), genetic amplification, (especially by PCR or LCR), double immunodiffusion technique, counter-electrophoresis technique, haemagglutination or a mixture thereof.

Another aspect of the present invention concerns a diagnosis method wherein a biological sample from the patient, such as cephalo-rachidian fluid, serum, blood, plasma, urine, broncho-alveolar lavage, stomach lavage, etc., is isolated from the patient, and is put in contact with the diagnostic device according to the invention for the diagnosis or the monitoring of an injury or a disease, preferably a lung injury or an oxidative stress-related disorder, affected by the presence of pro-oxidant agent or oxidative stress such as specific cardiovascular diseases like arteriosclerosis, neurodegenerative disorders (Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis), apoptosis, inflammatory reactions, allergic reactions such as asthma, hay fever and eczema, high bone mass syndrome, osteopetrosis, osteoporosis-pseudoglioma syndrome, and Bardet-Biedl syndrome 1. Said diagnosis and monitoring upon one or more biological samples obtained from several tissues from the patient can be advantageously obtained by one or more of the methods above-described, which could be adapted

according to the specific biological sample by the person skilled in the art.

Therefore, the product according to the invention could be used as a marker for the above-
5 identified injuries, diseases or disorders in a broad spectrum of tissues as shown in the enclosed Figure 1.

A further aspect of the present invention is related to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an element selected
10 from the group consisting of the nucleotide sequence, the amino acid sequence of the polypeptide according to the invention, the inhibitor directed against said sequences and/or one or more portions thereof.

A last aspect of the present invention is
15 related to the use of the pharmaceutical composition according to the invention for the manufacture of a medicament in the treatment and/or the prevention of lung injuries and/or diseases or of oxidative stress-related disorders.

The present invention is also related to a
20 prevention and/or treatment method of a patient, especially a human patient, preferably affected by lung injuries and/or diseases or by oxidative stress-related disorders, wherein a sufficient amount of the pharmaceutical
25 composition according to the invention is administered to said patient in order to treat, avoid and/or reduce the symptoms of said injuries and/or diseases.

Other injuries and/or diseases which can be prevented and/or treated are injuries and/or diseases
30 affected by the presence of pro-oxidant agents or oxidative stress, such as specific cardio-vascular diseases like arteriosclerosis, neurodegenerative disorders such as

Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, apoptosis and inflammatory reactions and some allergic reactions such as asthma, hay fever and eczema, high bone mass syndrome, osteopetrosis, 5 osteoporosis-pseudoglioma syndrome, and Bardet-Biedl syndrome 1.

The pharmaceutically acceptable carrier according to the invention is any compatible non-toxic substance suitable for administering the composition 10 according to the invention to a human patient. Pharmaceutically acceptable carriers according to the invention suitable for oral administration are the ones well known by the person skilled in the art, such as tablets, coated or non-coated pills, capsules, spray-gas, 15 patches, gels, solutions or syrups. Pharmaceutically acceptable carriers vary according to the mode of administration (intravenous, intramuscular, subcutaneous, parenteral, etc.), and may comprise also adjuvants well known by the person skilled in the art to increase, reduce 20 and/or regulate humoral, local and/or cellular response of the immune system.

The pharmaceutical composition according to the invention may be prepared by the methods, generally applied by the person skilled in the art in the preparation 25 of various pharmaceutical compositions, wherein the percentage of the active compound/pharmaceutically acceptable carrier can vary within very large ranges, only limited by the tolerance of the patient to said pharmaceutical composition, and wherein the limits are 30 particularly determined by the frequency of administration and the possible side-effects of the active compounds or its pharmaceutically acceptable carrier.

Another aspect of the invention is related to the use of the diagnostic device according to the invention for performing upon the patient or upon a biological fluid obtained from the patient, a diagnosis, a dosage and/or a
5 monitoring of the above-mentioned injuries or diseases or oxidative stress-related disorders affecting the patient.

A further aspect of the present invention is related to a cell or a non-human animal, preferably a mammal such as a mouse or a rat, transformed by the vector
10 according to the invention and overexpressing the polypeptide according to the invention, or a non-human animal, preferably a mammal such as a mouse or a rat, genetically modified by a partial or total deletion of its genomic sequence encoding the polypeptide according to the
15 invention (knock-out non-human mammal) and obtained by methods well known by the person skilled in the art such as the one described by Kahn et al. (*Cell*, Vol. 92, pp. 593-596 (March 1998)).

Other examples of genetically modified non-
20 human animals according to the invention may be a transgenic non-human animal comprising an inhibitor according to the invention, preferably an antisense nucleic acid sequence complementary to the nucleotide sequence according to the invention so placed as to be transcribed
25 into antisense mRNA which is complementary to the nucleotide sequence according to the invention and which hybridises to said nucleotide sequence, thereby reducing or blocking its translation.

Further aspects of the present invention will
30 be described in the enclosed non-limiting examples in reference to the following Figures.

Brief description of the drawings

- Figure 1 represents a dot blot analysis of mRNA encoding the polypeptide according to the invention in various types of human tissues.
- 5 Figure 2 represents a Northern blot analysis of mRNA encoding the polypeptide according to the invention in a rat lung after administration of lipopolysaccharides (LPS) inducing an inflammatory reaction of the lung.
- 10 Figure 3 represents a Northern blot analysis of mRNA encoding the polypeptide according to the invention in a rat lung after intraperitoneal injection of pneumotoxigants.
- Figure 4 is a schematic representation of the human genomic sequence, the complete cDNA sequence and the corresponding amino acid sequence.
- 15 Figure 5 represents respectively the alignment of the sequences of the human B18 polypeptide according to the invention with the corresponding rat and mouse sequences.
- 20

Example 1 : Homology between the B18 polypeptide according to the invention with other known nucleotide or amino acid sequences

- 25 The BLAST 2.0 software (gapped BLAST at the NCBI Internet site) was used for searching for homologies between human B18 (162 amino acids) and known polypeptides in databases (GenBank, SwissProt). Said search did not give perfect alignment with known peptides from different
- 30 species (Table 1). Homologies of the human B18 cDNA (805 nucleotides) with GenBank, EMBL, DDBJ and PDB deposited

nucleotide sequences (Table 2) and GenBank Expression Sequence TAGS (ESTs) were noted.

Table 1 : Homologies of the B18 proteins (162 amino acid) with other proteins

Name	NCBI ID	Identity (%) Homology (%)
Membrane protein (synechocystis sp.)	1652859	57/129 (44%) 81/129 (62%)
Peroxisomal-like protein (Aspergillus fumigatus)	2769700	56/176 (31%) 90/176 (50%)
Haein HI0572 hypothetical protein (Haemophilus influenzae)	1723174	53/146 (36%) 80/146 (54%)
PMP20 (Schizosaccharomyces pombe)	AJ002536	54/161 (33%) 85/161 (52%)
Peroxisomal membrane protein A (PMP 20) (Candida boidinii)	130360	59/170 (34%) 89/170 (51%)
Peroxisomal membrane protein B (PMP 20) (Candida boidinii)	130361	58/170 (34%) 88/170 (51%)
Putative peroxisomal protein PMP from yeast (Saccharomyces cerevisiae)	1709682	41/138 (29%) 72/138 (51%)
Alkylhydroperoxide reductase C22 protein (Escherichia coli)	P26427	36/126 (28%) 58/126 (45%)

Table 2

Name	Access NO	Identity
Human mRNA down-regulated in cells infected by adenovirus 5	U82616	259/263 (98%)
Human mRNA down-regulated in cells infected by adenovirus 5	U82615	300/321 (93%)

In the Table 2, an identity of 98% has been obtained with the alignment of 259 nucleotides of CDNA B18, which comprises in its totality 805 nucleotides, with 263 nucleotides of U82616 CDNA. A similar identity has been
5 obtained with the U82615 sequence.

The sequence SEQ ID NO 1 comprising 805 nucleotides presents a homology with several EST sequences obtained from a human and from a mouse, having the following references :

10 Human :

AA130751, N42215, W38597, N91311, N68467, AA187737,
N68916, W00593, R88950, AA181884, H20154, H66666

Mouse :

AA220019, AA123351, AA087129, AA255021, AA249897, W71344

15

Example 2 : Tissue detection

A human RNA master Blot (Clontech) containing 100-500 ng of poly-A + human RNA in each dot (normalised to the mRNA expression levels of eight different housekeeping
20 genes) was hybridised with a 554 bp-long B18 probe labelled with ³²P, and quantified, using Phosphorimaging Technology. As shown in Figure 1, B18 mRNA is present in all tissues examined but predominantly in trachea, lung, kidney, thyroid gland, stomach, colon, heart and some regions of
25 the brain. Highest expression has been noted in the thyroid tissue. This presence is probably correlated with the possible antioxidant activity of the B18 polypeptide according to the invention.

30 Example 3 : Inflammatory reaction

Figure 2 represents a Northern blot analysis of rat lung mRNA after 6, 48 and 72 hours after

lipopolysaccharides (LPS) instillation inducing an inflammatory reaction in the lung.

A Northern blot containing 15 μ g of total RNA in each lane was hybridised with a 225 bp-long rat B18 probe, stripped and reprobed with a 572 bp-long rat β -actin probe, both labelled with 32 P. Northern blot was quantified using Phosphorimaging Technology and the B18 mRNA data were normalised to β -actin mRNA level.

10 **Example 4 : Pneumotoxic reaction**

Figure 3 represents a Northern blot analysis of rat lung mRNA after intraperitoneal injection of pneumotoxicants (4-ipomeanol, 1-(3-furyl)-4-hydroxypentanone (IPO), methylcyclopentadienyl manganese tricarbonyl (MMT) or alpha naphthylthiourea (ANTU)). These agents are known to induce in the lung acute lesions of Clara (IPO) and alveolar cells (MMT) as well as increasing the permeability of the alveolar/blood barrier (ANTU). A Northern blot containing 15 μ g of total RNA in each lane was hybridised with a 225 bp-long rat B18 probe, stripped and reprobed with a 572 bp-long β -actin probe both labelled with 32 P. The Northern blot was quantified using Phosphorimaging Technology and rat B18 mRNA data were normalised to β -actin mRNA level.

25

Example 5 : Proteinic activity of the B18 polypeptide

An amino analysis of the complete human B18 amino acid sequence shows that said polypeptide presents specific portions showing an homology with other anti-oxidant enzymes (starting from a Leucine at position 36 until a Cysteine at position 47) and an other portion

having an important homology with beta chains of ATP synthase (starting from a Glutamic acid at position 13 until a Glycine in position 38).

Furthermore, the B18 amino acid sequence according to the invention shows an important homology with an *Aspergillus fumigatus* allergen (34% identity and 60% homology by using clustal V sequence alignment), especially upon the portion of said B18 polypeptide having possible antioxidant properties. Therefore, it is possible that a peroxisomal protein (possibly homologous to B18 protein) is able to induce and to bind IgE from patients sensitised to *Aspergillus fumigatus* peroxisomal proteins after an induction of the patient immune system with *Aspergillus fumigatus* allergen. This mechanism can be compared to a reaction obtained with the manganese superoxide dismutase (MnSOD) wherein the human MnSOD is able to bind to IgE from patients sensitised to *Aspergillus fumigatus* MnSOD.

Furthermore, the Inventors have identified a portion of the B18 human polypeptide which presents an homology with a Cyclophilin-binding domain of *Candida boidinii* PMP20 (receptor, of the immuno-suppressant drug cyclosporine A). Said possible Cyclophilin-binding domain is starting from the Threonine in position 150 until the Leucine in position 161.

25

Example 6 : B18 human gene and mRNA alternative splicing

As represented in the enclosed Figure 4, the Inventors have identified upon the genomic DNA (SEQ ID NO 10) 5 exons and 5 introns. By RT-PCR (using primers 5'-gggtatgggactagctggcg-3' and 5'-ctggccaacattccaattgcag-3') and according to the genomic sequence, 4 different cDNAs corresponding to the transcription of the said genomic DNA

have been identified in human lung and in human brain. A first cDNA of 736 bp corresponds to the cDNA encoding the complete amino acid sequence of the B18 protein according to the invention. However, 3 other cDNAs of 601, 604 and
5 469 bp were also identified, and comprise specific splicings of one or more exons.

Therefore, another aspect of the present invention is related to said specific portions of the complete genomic or CDNA nucleotide sequence according to
10 the invention or to specific portions of the complete amino acid sequence of the B18 protein according to the invention, which could be used also as specific markers of the B18 activity, preferably the anti-oxidative activity.

15 Example 7 : Knock-out mouse

Exons of a mouse genomic sequence encoding the B18 polypeptide according to the invention have been deleted by homologous recombination. Said homologous recombination has been obtained with a genetic sequence
20 comprising a neomycin resistant gene. The targeting vector with said gene and a ,thymidine kinase (in order to eliminate non-homologous recombinants with ganciclovir) has been prepared. Said recombination was used for the deletion of one or more exons of the B18 polypeptide. After
25 electroporation of ES cells with the targeting vector, positive clones having incorporated homologous recombination were identified by Southern blot with labelled probes. Aggregation of said positive clones with a morula from a Swiss pseudo-pregnant mouse produces several
30 chimeric mice which survive after birth. Several homozygote mice are obtained by cross-breeding and are used as a model for the above-mentioned diseases.

Similar experiments may be done with another mammal whose B18 sequence is known (the B18 sequence of a mouse and a rat and their alignment with the human sequence is shown in the enclosed Figure 5).

5

Example 8 : Chromosome localisation of human B18 gene

Radiation hybrid clones (GeneBridge 4 Radiation Hybrid Panel, Research Genetics) were used for performing chromosome localisation by PCR with two
10 different pairs of primers (5'-caggttcaccttggtccctggctc-3' (SEQ ID NO 14), 5'-atgttatgcaaccctttgcgacac-3' (SEQ ID NO 17) and 5'-gtgtttgaaggggagccaggggaac-3' (SEQ ID NO 18), 5'-agagacagggtttcaccatcttgg-3' (SEQ ID NO 19)).

The Inventors have located B18 genomic
15 sequence on human chromosome 11q13. B18 gene has been located 7.15-6.1 cR from marker D11S913 between markers D11S1963 and D11S4407 (Genome Database internet site).

Unknown genes linked to different disorders have been localised in the same region of chromosome 11.
20 Therefore, B18 gene is possibly associated with these disorders:

- atopy (atopic hypersensitivity: asthma, hay fever and eczema; MIM n°147050 at OMIM of NCBI internet site),
- high bone mass syndrome (MIM n°601884),
- 25 - osteopetrosis (MIM n°259700),
- osteoporosis-pseudoglioma syndrome (MIM n°259770) and
- Bardet-Biedl syndrome 1 (MIM n°209901).

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CLAIMS

1. Amino acid sequence having more than 70% homology with the sequence SEQ ID NO 2.

2. Amino acid sequence according to claim 1, having more than 85% homology with the sequence SEQ ID NO 2.

3. Amino acid sequence according to claim 1 or 2, having more than 95% homology with the sequence SEQ ID NO 2.

4. Amino acid sequence corresponding to SEQ ID NO 2 or a portion thereof selected from the group consisting of the sequences comprised between:

- the glutamic acid in position 13 and the glutamic acid in position 27,
- the alanine in position 26 and the leucine in position 36,
- the alanine in position 42 and the glutamic acid in position 57,
- the glutamic acid in position 57 and the valine in position 69,
- the valine in position 80 and the leucine in position 97,
- the arginine in position 95 and the leucine in position 112,
- the serine in position 118 and the serine in position 129,
- the valine in position 137 and the threonine in position 150,

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- the glutamic acid in position 13 and the cysteine in position 47,
- the glutamic acid in position 13 and the glycine in position 38, and
- 5 - the leucine in position 36 and the cysteine in position 47,
- and the treonine in position 150 and the leucine in position 161.

10 5. Nucleotide sequence encoding the amino acid sequence according to any one of the preceding claims and presenting more than 70% homology with SEQ ID NO 1 or its complementary strand.

15 6. Nucleotide sequence according to claim 5, having more than 85% homology with the sequence SEQ ID NO 1 or its complementary strand.

7. Nucleotide sequence according to claim 5 more than 95% homology with the sequence SEQ ID NO 1 or its complementary strand.

20 8. Nucleotide sequence corresponding to the sequence SEQ ID NO 1, its complementary strand or a portion thereof selected from the group consisting of SEQ ID n° 7, SEQ ID n° 8, SEQ ID n° 9, SEQ ID n° 11, SEQ ID n° 12, SEQ ID n° 13, SEQ ID n° 14, SEQ ID n° 15 and SEQ ID n° 16.

25 9. Vector comprising the nucleotide sequence according to any one of the claims 5 to 8.

10. Inhibitor directed against the amino acid or nucleotide sequence according to any one of the claims 1 to 8.

30 11. Inhibitor according to claim 10, being an antibody, preferably a monoclonal antibody, or a portion of said antibody.

12. Diagnostic device comprising an element selected from the group consisting of the amino acid

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sequence according to any one of the claims 1 to 4, the nucleotide sequence according to any one of the claims 5 to 8, the inhibitor according to claim 10 or 11, their portions or a mixture thereof.

5 13. Method for the in vitro detection of lung injuries and diseases or oxidative stress-related diseases and disorders, especially inflammatory diseases, comprising the steps of :

- 10 - isolating a sample from a body fluid of a patient, preferably a human patient,
- possibly inhibiting the contaminants present in said sample,
- put in contact said sample with an element selected from the group consisting of the amino acid sequence
- 15 according to any one of the claims 1 to 4, the nucleotide sequence according to any one of the claims 5 to 8, the inhibitor according to claim 10 or 11, their portions or a mixture thereof, and
- detecting a reaction of a molecule present in said
- 20 sample with said element.

14. Pharmaceutical composition comprising a pharmaceutically acceptable carrier and an element selected from the group consisting of the amino acid sequence according to any one of the claims 1 to 4, the nucleotide

25 sequence according to any one of the claims 5 to 8, the inhibitor according to claim 10 or 11, their portions or a mixture thereof.

15. Use of the pharmaceutical composition according to claim 14 for the manufacture of a medicament

30 for the prevention and/or the treatment of lung injuries or diseases, and of oxidative stress-related diseases or disorders, such as specific cardio-vascular diseases like arteriosclerosis, neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, amyotrophic

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lateral sclerosis, apoptosis and inflammatory reactions, allergic reactions such as asthma, hay fever and eczema, high bone mass syndrome, osteopetrosis, osteoporosis-pseudoglioma syndrome, and Bardet-Biedl syndrome 1.

5 16. Cell transformed by the vector according to claim 9 or comprising a total deletion of its nucleotide sequence according to any one of the claims 5 to 8.

10 17. Non-human animal, preferably a non-human mammal, transformed by the vector according to claim 9 or comprising a total deletion of its nucleotide sequence according to any one of the claims 5 to 8.

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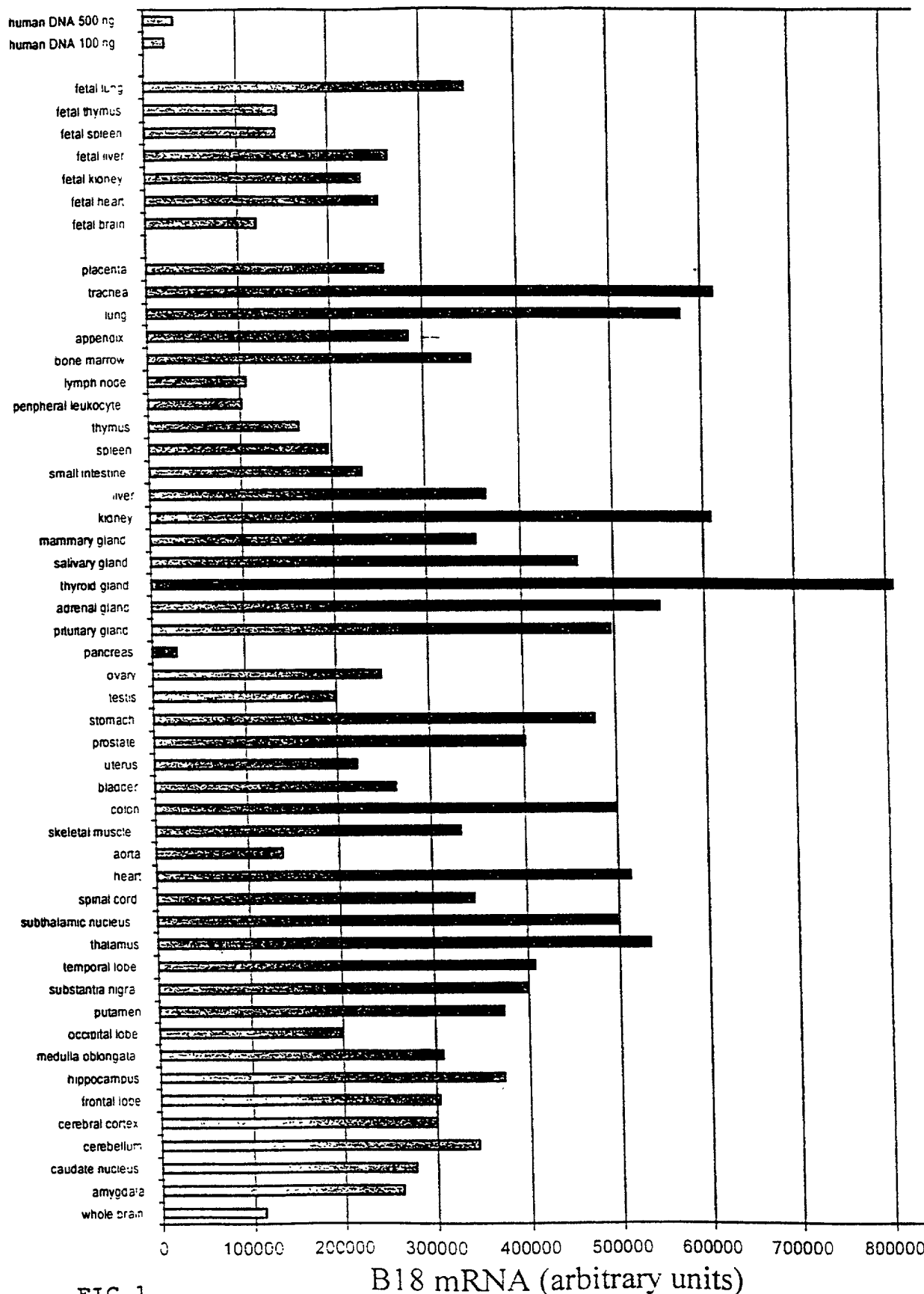


FIG. 1

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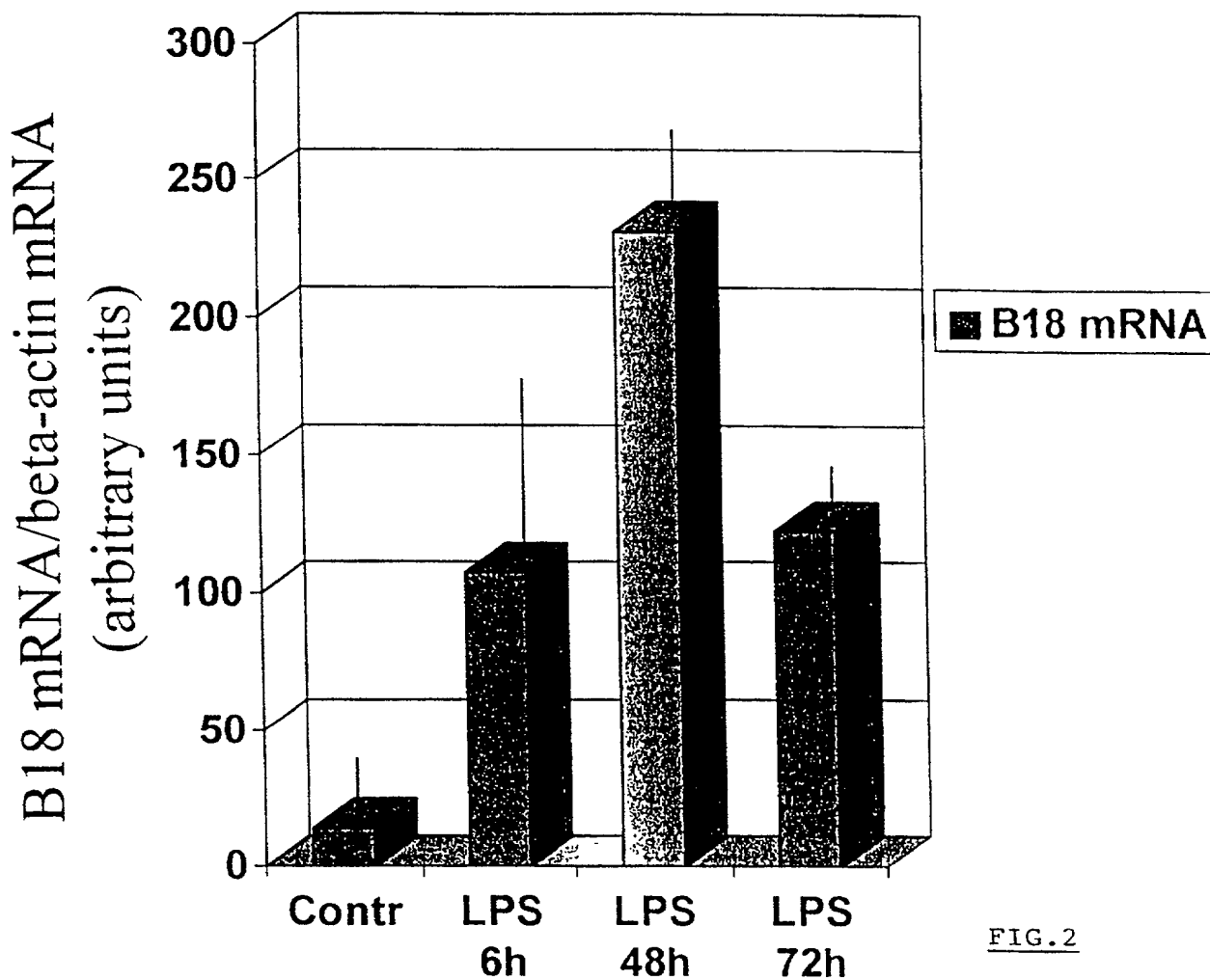
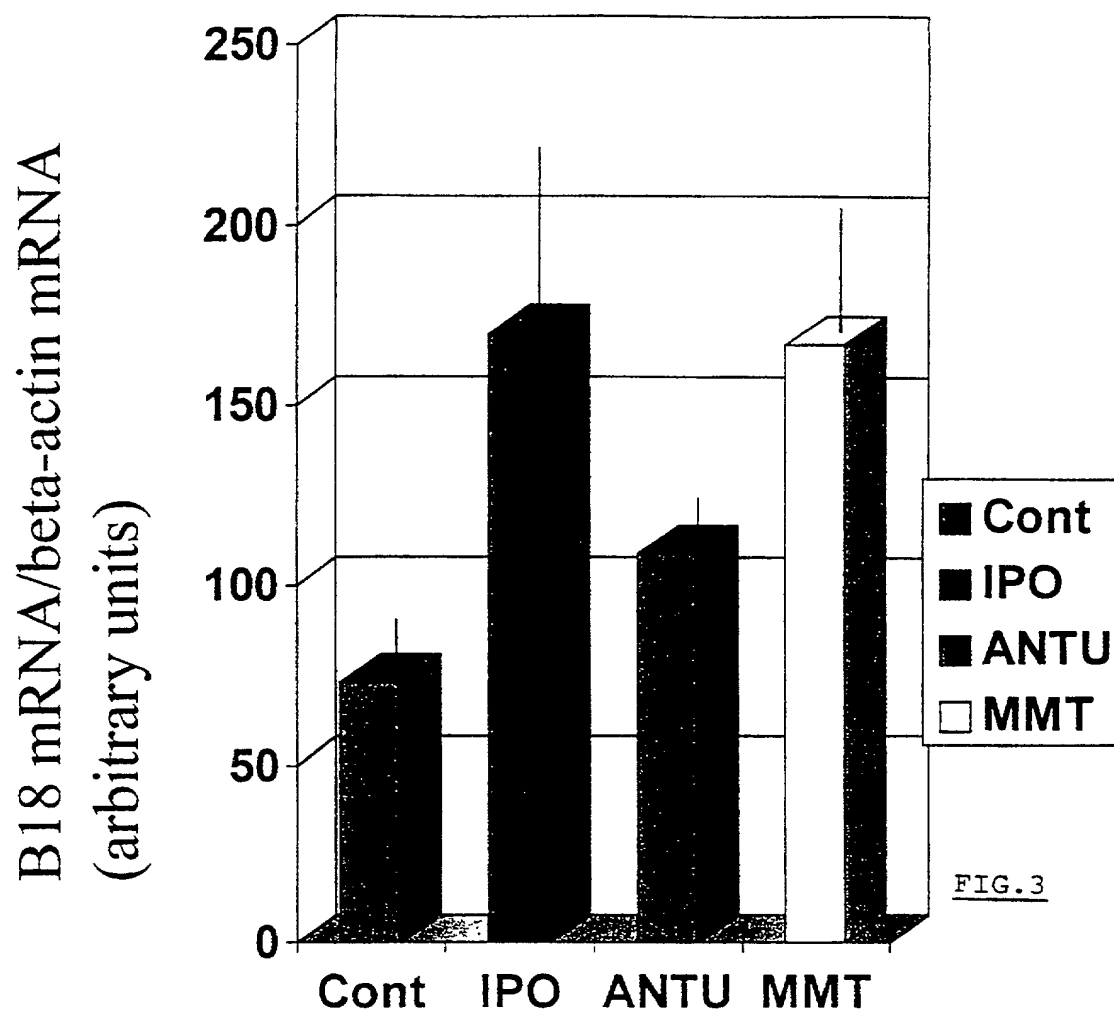
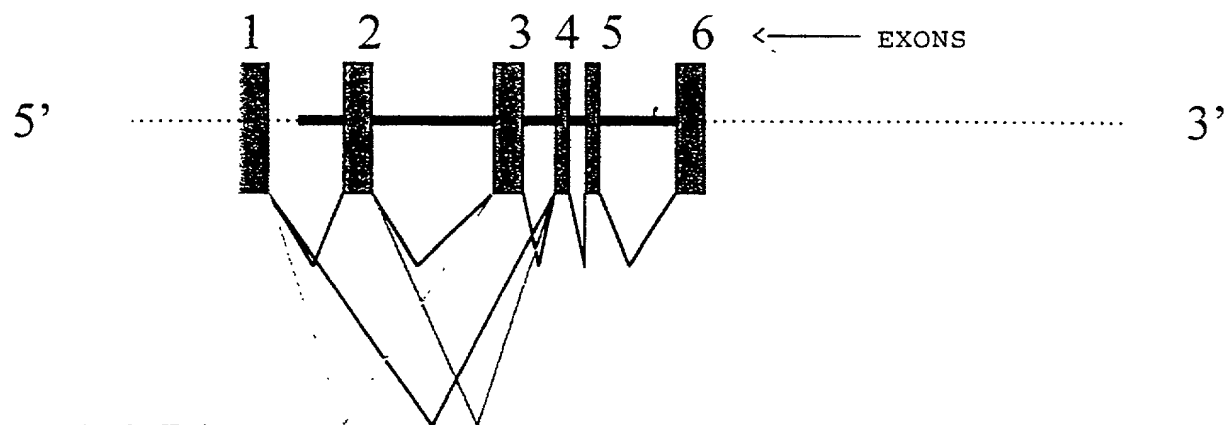


FIG. 2

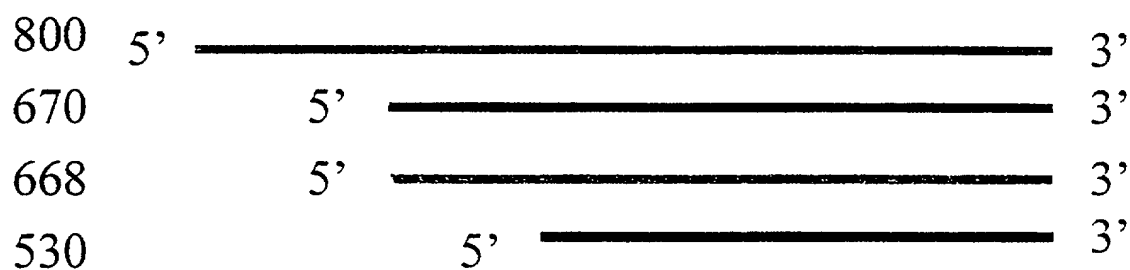
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Gene (chromosome 11q12-13)



mRNAs



Proteins

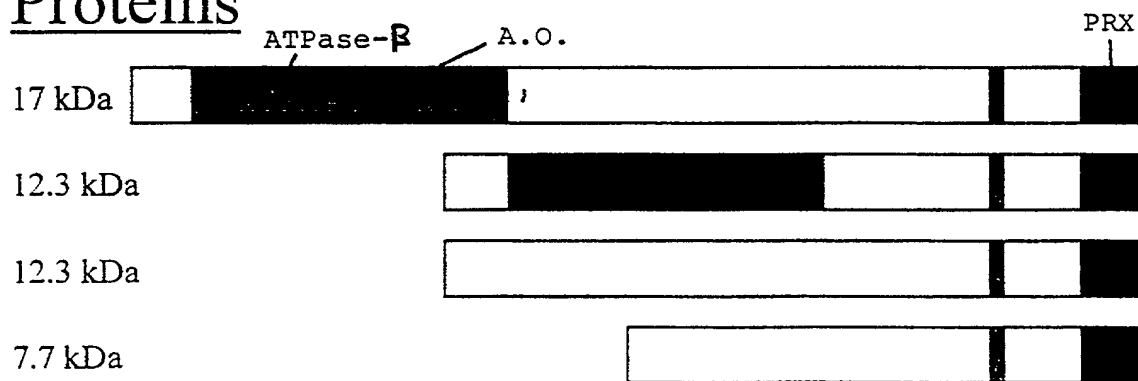


FIG. 4

CLUSTAL V alignment of human and rat B18 amino acid sequences (Identity: 90%, Homology: 97.5%):

B18hum	MAPIKVGDAIPAVEVFEGEPGNKVNLAELFKGKKGVLFVGPGAFTPGCSK	= SEQIDNO1
B18rat	MAPIKVGDTIP SVEVFEGEPGKKVNLAELFKDKKGVLFVGPGAFTPGCSK *****.*.*.*****.*****.*****.*****	
B18hum	THLPGFVEQAEALKAKGVQVACLSVNDAFVTGEWGRAHKAEGKVRLIAD	
B18rat	THLPGFVEQAGALKAKGAQVACLSVNDVFVTAEWGRAHQAEGKVQLIAD ***** ***** ***** **.******.*****.****	<u>FIG.5a</u>
B18hum	PTGAFGKETDLLLDDSLVSIFGNRRLLKRFSMVVDGIVKALNVEPDGTGL	
B18rat	PTGAFGKETDLLLDDSLVSLFGNRRLLKRFSMVIDKGVVKALNVEPDGTGL *****.*.*****.*.*.*****	
B18hum	TCSLAPNIISQL	
B18rat	TCSLAPNILSQL *****.*.*	

FIG. 5a

CLUSTAL V alignment of human and mouse B18 amino acid sequences (Identity: 91%, Homology: 96%):

```
B18hum          MAPIKVGDAIPAVEVFEGEPGNKVNLAELFKGKKGVLFQVPGAFTPGCSK
B18mouse        MAPIKVGDAIPSEVFEGEPGKKNVNLAELFKGKKGVLFQVPGAFTPGCSK
                *****_.*****_.*****.*****.*****.*****

B18hum          THLPGFVEQAEALKAKGVQVVACLSVNDAFVTGEWGRAHKAEGKVRLLDAD
B18mouse        THLPGFVEQAGALKAKGAQVVACLSVNDVFVIEEWGRAHQAEVKVRLLDAD
                ***** ***** ***** ** *****.*****.*****

B18hum          PTGAFGKETDLLLDDSLVSIFGNRRLKRFSMVVDGIVKALNVEPDGTGL
B18mouse        PTGAFGKATDLLLDDSLVSLFGNRRLKRFSMVIDNGIVKALNVEPDGTGL
                ***** *****.*****.....*****.*****

B18hum          TCSSLAPNIISQL
B18mouse        TCSSLAPNILSQL .
                ***** ***
```

CLUSTAL V alignment of human and rat cDNA sequences (identity: 612/780, 78.5%):

```

B18hum      GCCCAGGAGGCGGAGTGGAAAGTGGCCGTGGGGCGGGTATGGGACTAGCTGG
B18rat      -----TG-----CGTC-----CTAGGCAG
              **          ***          ****  *

B18hum      CGTGTGCGCCCTGAGACGCTCAGCGGGCTATATACTCGTCGGTGGGGCCG
B18rat      CATA---GCC---GGA---TCGGTGCTCCGTGCATCGGCTACTTGGAC--
              * *      ***      **      * * * * * * * * * * * * * * *

B18hum      GCGGTCAGTCTGCGGCAGCGGCAGCAAGACGGTGCAAGTGAAGGAGAGTGG
B18rat      -----GTGCGTGGCAGGCAGAGCAGGCCGG---AAAGGAGCAGGTTGG
              * *      * * * * *      * * * * *      * * * * * * * *

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FIG. 5b

B18hum	GCGTCTGGCGGGGTCCGCAGTTTTCAGCAGAGCCGCTGCAGCCATGGCCCC
B18rat	GAGTGTGGTGGGGCCCGCAGCTTCAGCAGTGCCGCGGTGACTATGGCCCC
	* * * * *
B18hum	AATCAAGGTGGGAGATGCCATCCAGCAGTGGAGGTGTTTGAAGGGGAGC
B18rat	GATCAAGGTGGGAGACACCATTCCCTCAGTGGAGGTATTTGAAGGGGAAC
	* * * * *
B18hum	CAGGGAACAAGGTGAACCTGGCAGAGCTGTTCAAGGGCAAGAAGGGTGTG
B18rat	CTGGAAAGAAGGTGAACCTGGCAGAGCTGTTCAAGGACAAGAAAGGTGTT
	* * * * *
B18hum	CTGTTTGGAGTTCCTGGGGCCTTCACCCCTGGATGTTCCAAGACACACCT
B18rat	TTGTTTGGAGTCCCTGGGGCATTTCACACCTGGCTGTTCCAAGACCCATCT
	* * * * *
B18hum	GCCAGGGTTTGTGGAGCAGGCTGAGGCTCTGAAGGCCAAGGGAGTCCAGG
B18rat	GCCTGGGTTTGTGGAGCAAGCCGGAGCTCTGAAGGCCAAGGGAGCACAAG
	* * * * *
B18hum	TGGTGGCCTGTCTGAGTGTTAATGATGCCTTTGTGACTGGCGAGTGGGGC
B18rat	TGGTGGCCTGTCTGAGTGTTAATGATGTCTTCGTGACTGCAGAGTGGGGT
	* * * * *
B18hum	CGAGCCCACAAGGCGGAAGGCAAGGTTTCGGCTCCTGGCTGATCCCCTG
B18rat	CGAGCCCACAGGCGGAAGGCAAGGTTTCAGCTCCTGGCTGACCCCCTG
	* * * * *
B18hum	GGCCTTTGGAAGGAGACAGACTTATTACTAGATGATTTCGTGGTGTCCA
B18rat	AGCTTTTGGAAAGGAGACAGATTTACTACTAGATGATTCTTTGGTGTCTC
	* * * * *
B18hum	TCTTTGGAATCGACGTCTCAAGAGGTTCTCCATGGTGGTACAGGATGGC
B18rat	TCTTTGGAATCGTCGGCTAAAAAGGTTCTCCATGGTGATAGACAAGGGC
	* * * * *
B18hum	ATAGTGAAGGCCCTGAATGTGGAACCAGATGGCACAGGCCTCACCTGCAG
B18rat	GTAATAAGGCACTGAACGTGGAGCCGGATGGCACAGGCCTCACCTGCAG
	* * * * *
B18hum	CCTGGCACCCAATATCATCTCACAGCTCTGAGGCCCTGGGCCAGATTACT
B18rat	CCTGGCCCCCAACATCCTCTCACAACTCTGAGGCCCTGA-CCAGA--ATG
	* * * * *
B18hum	TCCTCCACCCCTCCCTATCTCACCTGCCAGCCCTGTGCTGG-GGCCCTG
B18rat	TCCTCTGACTCTCCC-ATCTCCTCCACCCAGCTCTGGGCCAAAGGCCAG
	* * * * *
B18hum	CA-----ATTGGAATG-----TTGGCCAGATTCTGC
B18rat	TACCTCCTTACCTGAGGGCCACTGGAATGGAACCTTGACAATATTCTGC
	* * * * *
B18hum	AATAACACTTGTGGTTTGCGGAAAAAA-----
B18rat	AATAACAGTT-TAATTTGTGAAAAAAAAAAAAAAAAAAAA
	* * * * *

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CLUSTAL V alignment of human and mouse cDNA sequences (Identity: 552/675, 81.8%):

FIG.5c

```

B18hum      GCCAGGAGGCGGAGTGGAAAGTGGCCGTGGGGCGGGTATGGGACTAGCTGG
B18mouse    -----

B18hum      CGTGTGCGCCCTGAGACGCTCAGCGGGCTATATACTCGTCGGTGGGGCCG
B18mouse    -----TGCTCCGTG-----CATCGACGTGCTTG
                  **** * * * * * * * *

B18hum      GCGGTCACTCTGCGGCAGCGGCAGCAAGACGGTGCAGTGAAGGAGAGTGG
B18mouse    GCAGGCAG-----AGCAGGCCGG---AAAGAAGCAGGTTGG
                  * * * * * * * * * * * * * *

B18hum      GCGTCTGGCGGGGTCCGCAGTTTCAGCAGAGCCGCTGCAGCCATGGCCCC
B18mouse    GAGTGTGGCGGAGCCCCGCAGCTTCAGCAGCTCCGCGGTGACCATGGCCCC
                  * * * * * * * * * * * * * *

B18hum      AATCAAGGTGGGAGATGCCATCCCAGCAGTGGAGGTGTTTGAAGGGGAGC
B18mouse    GATCAAGGTGGGAGATGCCATTCCCTCAGTGGAGGTATTTGAAGGGGAAC
                  * * * * * * * * * * * * * *

B18hum      CAGGGAACAAGGTGAACCTGGCAGAGCTGTTCAAGGGCAAGAAGGGTGTG
B18mouse    CGGGAAAGAAGGTGAACCTGGCAGAGCTGTTCAAGGGCAAGAAAGGTGTT
                  * * * * * * * * * * * * * *

B18hum      CTGTTTGGAGTTCCTGGGGCCTTCACCCCTGGATGTTCCAAGACACACCT
B18mouse    TTGTTTGGAGTCCCTGGGGCATTACACCTGGCTGTTCTAAGACCCACCT
                  * * * * * * * * * * * * * *

B18hum      GCCAGGGTTTGTGGAGCAGGCTGAGGCTCTGAAGGCCAAGGGAGTCCAGG
B18mouse    GCCTGGGTTTGTGGAGCAAGCTGGAGCTCTGAAGGCTAAGGGAGCGCAGG
                  * * * * * * * * * * * * * *

B18hum      TGGTGGCCTGTCTGAGTGTTAATGATGCCTTTGTGACTGGCGAGTGGGGC
B18mouse    TGGTGGCCTGTCTGAGCGTTAATGACGTCTTTGTGATTGAAGAGTGGGGT
                  * * * * * * * * * * * * * *

B18hum      CGAGCCCACAAGGCGGAAGGCAAGGTTGCGCTCCTGGCTGATCCCACTGG
B18mouse    CGAGCCCACCAAGGCGGAAGGCAAGGTTGCGCTCCTGGCTGACCCCACTGG
                  * * * * * * * * * * * * * *

B18hum      GGCCTTTGGGAAGGAGACAGACTTATTACTAGATGATTGCTGGTGTCCA
B18mouse    AGCCTTTGGGAAGGCGACAGACTTATTATTGGATGATTCTTTGGTGTCTC
                  * * * * * * * * * * * * * *

B18hum      TCTTTGGGAATCGACGTCTCAAGAGGTTCTCCATGGTGGTACAGGATGGC
B18mouse    TCTTTGGGAATCGTGGCTGAAAAGGTTCTCCATGGTGTAGACAACGGC
                  * * * * * * * * * * * * * *

B18hum      ATAGTGAAGGCCCTGAATGTGGAACCAGATGGCACAGGCCTCACCTGCAG
B18mouse    ATAGTGAAGGCACTGAACGTGGAGCCAGATGGCACAGGCCTCACCTGCAG
                  * * * * * * * * * * * * * *

B18hum      CCTGGCACCCCAATATCATCTCACAGCTCTGAGGCCCTGGGCCAGATTACT
B18mouse    CCTGGCCCCCAACATCCTCTCCCACTCTGAGGCCCTGG-CCAGATG---
                  * * * * * * * * * * * * * *

B18hum      TCCTCCACCCCTCCCTATCTCACCTGCCAGCCCTGTGCTGGGGCCCTGC
B18mouse    TCCTCTGACTCTCC-ATCTCTCCACCCGGCTCT-----AGGCC---
                  * * * * * * * * * * * * * *

B18hum      AATTGGAATGTTGGCCAGATTTCTGCAATAAACACTTGTGGTTTGGCGAA
B18mouse    -----AAAAGGCTCGGTACCTCCTTACTGGGAGC-CACGT-----
                  * * * * * * * * * * * * * *

```

1
SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:

(A) NAME: UNIVERSITE CATHOLIQUE DE LOUVAIN
Halles Universitaires
(B) STREET: Place de l' Universite, 1
(C) CITY: LOUVAIN-LA-NEUVE
(E) COUNTRY: BELGIUM
(F) POSTAL CODE (ZIP): B-1348

(A) NAME: UNIVERSITE DE MONS-HAINAUT
(B) STREET: Place du Parc 20
(C) CITY: MONS
(E) COUNTRY: BELGIUM
(F) POSTAL CODE (ZIP): B-7000

(ii) TITLE OF INVENTION: PEROXISOME-ASSOCIATED PEPTIDE, NUCLEOTIDE
SEQUENCE ENCODING SAID PEPTIDE AND THEIR USES IN THE
DIAGNOSTIC AND/OR THE TREATMENT OF LUNG INJURIES AND
DISEASES, AND OF OXIDATIVE STRESS-RELATED DISORDERS

(iii) NUMBER OF SEQUENCES: 19

(iv) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPO)

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 805 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 193..681

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

GCCAGGAGGC GGAGTGGAAAG TGGCCGTGGG GCGGGTATGG GACTAGCTGG CGTGTGCGCC	60
CTGAGACGCT CAGCGGGCTA TATACTCGTC GGTGGGGCCG GCGGTCAGTC TGCGGCAGCG	120

2

GCAGCAAGAC GGTGCAGTGA AGGAGAGTGG GCGTCTGGCG GGGTCCGCAG TTTCAGCAGA	180
GCCGCTGCAG CC ATG GCC CCA ATC AAG GTG GGA GAT GCC ATC CCA GCA	228
Met Ala Pro Ile Lys Val Gly Asp Ala Ile Pro Ala	
1 5 10	
GTG GAG GTG TTT GAA GGG GAG CCA GGG AAC AAG GTG AAC CTG GCA GAG	276
Val Glu Val Phe Glu Gly Glu Pro Gly Asn Lys Val Asn Leu Ala Glu	
15 20 25	
CTG TTC AAG GGC AAG AAG GGT GTG CTG TTT GGA GTT CCT GGG GCC TTC	324
Leu Phe Lys Gly Lys Lys Gly Val Leu Phe Gly Val Pro Gly Ala Phe	
30 35 40	
ACC CCT GGA TGT TCC AAG ACA CAC CTG CCA GGG TTT GTG GAG CAG GCT	372
Thr Pro Gly Cys Ser Lys Thr His Leu Pro Gly Phe Val Glu Gln Ala	
45 50 55 60	
GAG GCT CTG AAG GCC AAG GGA GTC CAG GTG GTG GCC TGT CTG AGT GTT	420
Glu Ala Leu Lys Ala Lys Gly Val Gln Val Val Ala Cys Leu Ser Val	
65 70 75	
AAT GAT GCC TTT GTG ACT GGC GAG TGG GGC CGA GCC CAC AAG GCG GAA	468
Asn Asp Ala Phe Val Thr Gly Glu Trp Gly Arg Ala His Lys Ala Glu	
80 85 90	
GGC AAG GTT CGG CTC CTG GCT GAT CCC ACT GGG GCC TTT GGG AAG GAG	516
Gly Lys Val Arg Leu Leu Ala Asp Pro Thr Gly Ala Phe Gly Lys Glu	
95 100 105	
ACA GAC TTA TTA CTA GAT GAT TCG CTG GTG TCC ATC TTT GGG AAT CGA	564
Thr Asp Leu Leu Leu Asp Asp Ser Leu Val Ser Ile Phe Gly Asn Arg	
110 115 120	
CGT CTC AAG AGG TTC TCC ATG GTG GTA CAG GAT GGC ATA GTG AAG GCC	612
Arg Leu Lys Arg Phe Ser Met Val Val Gln Asp Gly Ile Val Lys Ala	
125 130 135 140	
CTG AAT GTG GAA CCA GAT GGC ACA GGC CTC ACC TGC AGC CTG GCA CCC	660
Leu Asn Val Glu Pro Asp Gly Thr Gly Leu Thr Cys Ser Leu Ala Pro	
145 150 155	
AAT ATC ATC TCA CAG CTC TGA GGCCCTGGGC CAGATTACTT CCTCCACCCC	711
Asn Ile Ile Ser Gln Leu *	
160	
TCCCTATCTC ACCTGCCAG CCCTGTGCTG GGGCCCTGCA ATTGGAATGT TGGCCAGATT	771
TCTGCAATAA ACACTTGTGG TTTGCGGAAA AAAA	805

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 163 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

3

```

Met Ala Pro Ile Lys Val Gly Asp Ala Ile Pro Ala Val Glu Val Phe
 1           5           10           15
Glu Gly Glu Pro Gly Asn Lys Val Asn Leu Ala Glu Leu Phe Lys Gly
          20           25           30
Lys Lys Gly Val Leu Phe Gly Val Pro Gly Ala Phe Thr Pro Gly Cys
          35           40           45
Ser Lys Thr His Leu Pro Gly Phe Val Glu Gln Ala Glu Ala Leu Lys
          50           55           60
Ala Lys Gly Val Gln Val Val Ala Cys Leu Ser Val Asn Asp Ala Phe
          65           70           75           80
Val Thr Gly Glu Trp Gly Arg Ala His Lys Ala Glu Gly Lys Val Arg
          85           90           95
Leu Leu Ala Asp Pro Thr Gly Ala Phe Gly Lys Glu Thr Asp Leu Leu
          100          105          110
Leu Asp Asp Ser Leu Val Ser Ile Phe Gly Asn Arg Arg Leu Lys Arg
          115          120          125
Phe Ser Met Val Val Gln Asp Gly Ile Val Lys Ala Leu Asn Val Glu
          130          135          140
Pro Asp Gly Thr Gly Leu Thr Cys Ser Leu Ala Pro Asn Ile Ile Ser
          145          150          155          160
Gln Leu *
```

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 780 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Rattus Rattus

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 136..624

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

```

TGCGTCTTAG GCAGCATAGC CGGATCGGTG CTCCGTGCAT CGGCTACTTG GACGTGCGTG      60
GCAGGCAGAG CAGGCCGGAA AGGAGCAGGT TGGGAGTGTG GTGGGGCCCG CAGCTTCAGC      120
```

4

AGTGCCGCGG TGA CTATGGC CCCGATCAAG GTGGGAGACA CCATTCCCTC AGTGGAGGTA 180
TTTGRAGGGG AACCTGGAAA GAAGGTGAAC TTGGCAGAGC TGTTCAGGA CAAGAAAGGT 240
GTTTTGTTTG GAGTCCCTGG GGCATTTACA CCTGGCTGTT CCAAGACCCA TCTGCCTGGG 300
TTTGTGGAGC AAGCCGGAGC TCYGAAGGCC AAGGGAGCAC AAGTGGTGGC CTGTCTGAGT 360
GTTAATGATG YCTTCGTGAC TGCAGAGTGG GGTCTGAGCCC ACCAGGCAGA AGGCAAGGTT 420
CAGCTCCTGG CTGACCCAC TGGAGCTTTT GGAAAGGAGA CAGATTTACT ACTAGATGAT 480
TCTTTGGTGT CTCTCTTTGG GAATCGTCGG CTAAAAAGGT TCTCCATGGT GATAGACAAG 540
GGCGTAGTAA AGGCACTGAA CGTGGAGCCG GATGGCACAG GCCTCACCTG CAGCCTGGCC 600
CCCAACATCC TCTCACA ACT CTGAGGCCCT GACCAGAATG TCCTCTGACT CTCCCATCTC 660
CTCCACCCAG CTCTGGGCCA AAGGCCCAGT ACCTCCTTAC CTGAGGGCCA CTGGAATGGA 720
ACCTTGACAA TATTTCTGCA ATAAACAGTT TAATTTGTGA AAAAAAAAAA AAAAAAAAAA 780

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 162 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Rattus Rattus

(ix) FEATURE:

- (A) NAME/KEY: Modified-site
- (B) LOCATION:17
- (D) OTHER INFORMATION:/product= "Glu or Gly"

(ix) FEATURE:

- (A) NAME/KEY: Modified-site
- (B) LOCATION:63
- (D) OTHER INFORMATION:/product= "Leu or Pro"

(ix) FEATURE:

- (A) NAME/KEY: Modified-site
- (B) LOCATION:79
- (D) OTHER INFORMATION:/product= "Ala or Val"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Met Ala Pro Ile Lys Val Gly Asp Thr Ile Pro Ser Val Glu Val Phe
1 5 10 15

5

Xaa Gly Glu Pro Gly Lys Lys Val Asn Leu Ala Glu Leu Phe Lys Asp
 20 25 30
 Lys Lys Gly Val Leu Phe Gly Val Pro Gly Ala Phe Thr Pro Gly Cys
 35 40 45
 Ser Lys Thr His Leu Pro Gly Phe Val Glu Gln Ala Gly Ala Xaa Lys
 50 55 60
 Ala Lys Gly Ala Gln Val Val Ala Cys Leu Ser Val Asn Asp Xaa Phe
 65 70 75 80
 Val Thr Ala Glu Trp Gly Arg Ala His Gln Ala Glu Gly Lys Val Gln
 85 90 95
 Leu Leu Ala Asp Pro Thr Gly Ala Phe Gly Lys Glu Thr Asp Leu Leu
 100 105 110
 Leu Asp Asp Ser Leu Val Ser Leu Phe Gly Asn Arg Arg Leu Lys Arg
 115 120 125
 Phe Ser Met Val Ile Asp Lys Gly Val Val Lys Ala Leu Asn Val Glu
 130 135 140
 Pro Asp Gly Thr Gly Leu Thr Cys Ser Leu Ala Pro Asn Ile Leu Ser
 145 150 155 160
 Gln Leu

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 675 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Mouse

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 99..588

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

TGCTCCGTGC ATCGACGTGC TTGGCAGGCA GAGCAGGCCG GAAAGAAGCA GGTGGGGAGT	60
GTGGCGGAGC CCGCAGCTTC AGCAGCTCCG CGGTGACCAT GGCCCCGATC AAGGTGGGAG	120
ATGCCATTCC CTCAGTGGAG GTATTTGAAG GGGAAACGGG AAAGAAGGTG AACTTGGCAG	180
AGCTGTTCAA GGGCAAGAAA GGTGTTTTGT TTGGAGTCCC TGGGGCATT T ACACCTGGCT	240

```

GTTCTAAGAC CCACCTGCCT GGGTTTGTGG AGCAAGCTGG AGCTCTGAAG GCTAAGGGAG      300
CGCAGGTGGT GGCCTGTCTG AGCGTTAATG ACGTCTTTGT GATTGAAGAG TGGGGTCGAG      360
CCCACCAGGC AGAAGGCAAG GTTCGGCTCC TGGCTGACCC CACTGGAGCC TTTGGGAAGG      420
CGACAGACTT ATTATTGGAT GATTCTTTGG TGTCTCTCTT TGGGAATCGT CGGCTGAAAA      480
GGTTCTCCAT GGTGATAGAC AACGGCATAG TGAAGGCACT GAACGTGGAG CCAGATGGCA      540
CAGGCCTCAC CTGCAGCCTG GCCCCAACA TCCTCTCCCA ACTCTGAGGC CCTGGCCAGA      600
TGTCTCTGA CTCTCCCATC TCTCCACCC GGCTCTAGGC CAAAAGGCTC GGTACCTCCT      660
TACTGGGAGC CACGT                                                    675

```

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 162 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Mouse

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

```

Met Ala Pro Ile Lys Val Gly Asp Ala Ile Pro Ser Val Glu Val Phe
1           5           10           15
Glu Gly Glu Pro Gly Lys Lys Val Asn Leu Ala Glu Leu Phe Lys Gly
20           25           30
Lys Lys Gly Val Leu Phe Gly Val Pro Gly Ala Phe Thr Pro Gly Cys
35           40           45
Ser Lys Thr His Leu Pro Gly Phe Val Glu Gln Ala Gly Ala Leu Lys
50           55           60
Ala Lys Gly Ala Gln Val Val Ala Cys Leu Ser Val Asn Asp Val Phe
65           70           75           80
Val Ile Glu Glu Trp Gly Arg Ala His Gln Ala Glu Gly Lys Val Arg
85           90           95
Leu Leu Ala Asp Pro Thr Gly Ala Phe Gly Lys Ala Thr Asp Leu Leu
100          105          110
Leu Asp Asp Ser Leu Val Ser Leu Phe Gly Asn Arg Arg Leu Lys Arg
115          120          125

```

Phe Ser Met Val Ile Asp Asn Gly Ile Val Lys Ala Leu Asn Val Glu
 130 135 140

Pro Asp Gly Thr Gly Leu Thr Cys Ser Leu Ala Pro Asn Ile Leu Ser
 145 150 155 160

Gln Leu

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 469 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Homo sapiens

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION:161..382

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

```

GGGTATGGGA CTAGCTGGCG TGTGCGCCCT GAGACGCTCA GCGGGCTATA TACTCGTCGG      60
TGGGGCCGGC GGTCACTCTG CGGCAGCGGC AGCAAGACGG TGCAGTGAAG GAGAGTGGGC      120
GTCTGGCGGG GTCCGCAGTT TCAGCAGAGC CGCTGCAGCC ATGGCCCCAA TCAAGGTTTC      180
GCTCCTGGCT GATCCCACTG GGGCCTTTGG GAAGGAGACA GACTTATTAC TAGATGATTC      240
GCTGGTGTCC ATCTTTGGGA ATCGACGTCT CAAGAGGTTT TCCATGGTGG TACAGGATGG      300
CATAGTGAAG GCCCTGAATG TGGAACCAGA TGGCACAGGC CTCACCTGCA GCCTGGCACC      360
CAATATCATC TCACAGCTCT GAGGCCCTGG GCCAGATTAC TTCCTCCACC CCTCCCTATC      420
TCACCTGCCC AGCCGTGTGC TGGGGCCCTG CAATTGGAAT GTTGCCAG      469
  
```

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 601 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION:161..514

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

```
GGGTATGGGA CTAGCTGGCG TGTGCGCCCT GAGACGCTCA GCGGGCTATA TACTCGTCGG      60
TGGGGCCGGC GGTCAGTCTG CGGCAGCGGC AGCAAGACGG TGCAAGTGAAG GAGAGTGGGC      120
GTCTGGCGGG GTCCGCAGTT TCAGCAGAGC CGCTGCAGCC ATGGCCCCAA TCAAGACACA      180
CCTGCCAGGG TTTGTGGAGC AGGCTGAGGC TCTGAAGGCC AAGGGAGTCC AGGTGGTGGC      240
CTGTCTGAGT GTTAATGATG CCTTTGTGAC TGGCGAGTGG GGCCGAGCCC ACAAGGCGGA      300
AGGCAAGGTT CGGCTCCTGG CTGATCCAC TGGGGCCTTT GGAAGGAGA CAGACTTATT      360
ACTAGATGAT TCGCTGGTGT CCATCTTTGG GAATCGACGT CTCAAGAGGT TCTCCATGGT      420
GGTACAGGAT GGCATAGTGA AGGCCCTGAA TGTGGAACCA GATGGCACAG GCCTCACCTG      480
CAGCCTGGCA CCAATATCA TCTCACAGCT CTGAGGCCCT GGGCCAGATT ACTTCCTCCA      540
CCCCTCCCTA TCTCACCTGC CCAGCCCTGT GCTGGGGCCC TGCAATTGGA ATGTTGGCCA      600
G                                                                           601
```

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 604 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION:161..517

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

```
GGGTATGGGA CTAGCTGGCG TGTGCGCCCT GAGACGCTCA GCGGGCTATA TACTCGTCGG      60
```

9

TGGGGCCGGC	GGTCAGTCTG	CGGCAGCGGC	AGCAAGACGG	TGCAGTGAAG	GAGAGTGGGC	120
GTCTGGCGGG	GTCCGCAGTT	TCAGCAGAGC	CGCTGCAGCC	ATGGCCCCAA	TCAAGGTGGG	180
AGATGCCATC	CCAGCAGTGG	AGGTGTTTGA	AGGGGAGCCA	GGGAACAAGG	TGAACCTGGC	240
AGAGCTGTTC	AAGGGCAAGA	AGGGTGTGCT	GTTTGGAGTT	CCTGGGGCCT	TCACCCCTGG	300
ATGTTCCAAG	GTTTCGGCTCC	TGGCTGATCC	CACTGGGGCC	TTTGGGAAGG	AGACAGACTT	360
ATTACTAGAT	GATTCGCTGG	TGTCCATCTT	TGGGAATCGA	CGTCTCAAGA	GGTTCTCCAT	420
GGTGGTACAG	GATGGCATAG	TGAAGGCCCT	GAATGTGGAA	CCAGATGGCA	CAGGCCCTCAC	480
CTGCAGCCTG	GCACCCAATA	TCATCTCACA	GCTCTGAGGC	CCTGGGCCAG	ATTACTTCCT	540
CCACCCCTCC	CTATCTCACC	TGCCAGCCCC	TGTGCTGGGG	CCCTGCAATT	GGAATGTTGG	600
CCAG						604

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2710 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Homo sapiens

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:2516..2710

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:2074..2135

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:1932..1970

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:1728..1859

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:802..936

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

TCTGTCCCTT AGCGCCCCCG CGGGGGCTTA CCCCATCCCA CTCCATGACC TCCCCTCCCC	60
CCATGGCGAA TTCCCACCTT TCTGTCTTTC ACTCACTTCC TGGAACCGTC CCCAGGGCCT	120
TGGACCTTCC CCCTTCTCCT CCCAAACCTT GTGAGACCCC ATTCCCTTTC TACTTCATCC	180
TGCTCTCAAC TTTTGGGCTC CTCAGAGGCC CTCACCCCTG ACTCTCTCTC CCTACCCACT	240
CTGGTCCCAT GAAGCCCTCA AGTACTCTGG GGATGGATCC TTCCCCCTTC AAAAGATTCC	300
TTCTTTTGT CTACACCTCC TGGGTGTAGG GGCCTGGACA CCCTCCCCCA ACGTTCACCC	360
TGCCGCTGCC CTTCCTCTTC CTCCTCCTGA GGGTGGGACC CTCAGACCTG GCCAAGATCC	420
TCTCCCTCCA TGTTGTCAGG GACTCCTCCT CACCCCCAAA TACAGCCCTC TAGCCCCTGT	480
CCATTTTATT CCACTCCTTT CCTGTAACCT AGACAGCATG TTATGCAACC CTTTGCGACA	540
CATGGGGAAA CCTTCCCTCC CTTCCTCTGT TGTCACCAAT GGCCCTTAA GAGGAGCAGG	600
GCCACCTTGA AACTTGGAGG ATATGGGGTA ACCCAGTGGG AGCGGGCAGG GAGGGCCCTT	660
GGAAACTGAC AGGGCTGGAG TATCCTGCTG GGTTCAGCC CCGGTTCCTG CAGGCACAGC	720
TGCCAGGCTC TCTGTTCACT TTCCTGCCTC TGGTTTGCCC CGGCTCCCTC ACCCCCCTTA	780
CCCTGGAGTC CTTCTTCTA GGTGGGAGAT GCCATCCCAG CAGTGGAGGT GTTTGAAGGG	840
GAGCCAGGGA ACAAGGTGAA CCTGGCAGAG CTGTTCAAGG GCAAGAAGGG TGTGCTGTTT	900
GGAGTTCCTG GGGCCTTCAC CCCTGGATGT TCCAAGGTGA GGCCCTTCCC CTTCTGAAGA	960
TCAGGACCTG GGGATCTTTT GTGTTGCTCT TAAGTCTCC ACATAGTCCT GATAGGACTC	1020
CTAAAAAGCA TTTCAGTGCC ATCACAAAAC AAGTAGAGCT GGGTAGAGCT GGGCGCGGTG	1080
GCTCACGCCT GTAATCCCAG CACTTTGGGA GGCCAAGGCG GGTGGATCAC GAGGTCAGGA	1140
GTCCAAAACC AGCCTGGCCA AGATGGTGAA ACCCTGTCTC TACTAAAAAT GCAAAAAAAT	1200
CAGCCGGATA TGGTGGCGGG CGCCTGTAAT CCCAGGTATT GGGGAGGCTG AGGCAGAGAA	1260
TTGCTTGAAC CCAGGAGGCG TAGGTTGCAG TGAGTGGAGA TCGTGCCTCT GCAGTCCAGC	1320
CTGGGTGAAA GAGCGAGACT CCGTCTCAA ATGAAAAAAA AAAAGAAAA CAAGTAGAGA	1380
CTGCAAAAAG GGAACAGTAC CGGGAATGTT GGAGAAAAAC ATACTACAAT TAAATCCAAC	1440
ACCCCTGTTG GTCCTGCTAA ATGACAGGCA CTGTGGAAGG TGCTTGGGAC TCAGATAAAT	1500
AAGACAAAGA TCTGCCCATG GAAAGTTCAC GTCTGGACCA TAAGGCATTA GGTTTCATTC	1560
TGAGCTTCCT AGTGGCCAAG GCAAAAAGGA AATAGAATGG TTAGACAGC TCTCATTGTC	1620
TGATCAAAGG TGTTGAGGCA GAGCACTGAG GAGGGCCTGG AGATAAAGGG TGGGCTGGGG	1680
GTCAGATGCA GTTATCCCTT TGCCGACCCT TTGTTCCCCT TCCTCAGACA CACCTGCCAG	1740
GGTTTGTGGA GCAGGCTGAG GCTCTGAAGG CCAAGGGAGT CCAGGTGGTG GCCTGTCTGA	1800
GTGTTAATGA TGCCTTTGTG ACTGGCGAGT GGGGCCGAGC CCACAAGGCG GAAGGCAAGG	1860

TGAGGTGAGG GGCCTGCAGG GAGTCAGGAC CAGGTAGGAT ATTCTTCTTG TGACCTCTAC 1920
TTTCTCTGCA GGTTCGGCTC CTGGCTGATC CCACTGGGGC CTTTGGGAAG GTGAGTGTTC 1980
CCCTGACCGC CACAGGGACA TGGCGGTGCG GGGAGCAGTG GGGGCCCTTG GCCTCTTCAA 2040
GGATTTCTGA CACTTTTCTC TGTCTCTTCT TAGGAGACAG ACTTATTACT AGATGATTCTG 2100
CTGGTGTCCA TCTTTGGGAA TCGACGTCTC AAGAGGTAAA AGTGGAGAGT CCTCTGTGGA 2160
GAAAGTCCTC TGTGGGAGAG AGTCCTCTGT GGGAGAGAGT CCTCTGTGGA GAGGGTCCTC 2220
TGTGGGAAGA GTCGTCTGTG GGGGAGATGT GTGGGAGAGA GTCCTGTGTG GGGAGAGTCT 2280
TCTGTAGGGG AGAGTCCTCT GGGGAGAGAG TCCTGTGTGG GGGAGAGTCC TCTGTGGGGA 2340
GAGTCCTCTG TGTGGAGAGA GTCCTGTGTG GTGGTGAGTC CTCTGTGGGG GAGAGTCCTC 2400
TGTGGGGGGA GTCCTCTCTG GAGTTCTCTT GGGCCCCTGG CTGTTCACTG CCTGTCTCCA 2460
TGCCCAGCCT CCAAGCCCAG GCTGATGCAG CTGGCTGGGC CCCTCTTTCC GGCAGGTTCT 2520
CCATGGTGGT ACAGGATGGC ATAGTGAAGG CCCTGAATGT GGAACCAGAT GGCACAGGCC 2580
TCACCTGCAG CCTGGCACCC AATATCATCT CACAGCTCTG AGGCCCTGGG CCAGATTACT 2640
TCCTCCACCC CTCCTATCT CACCTGCCCA GCCCTGTGCT GGGGCCCTGC AATTGGAATG 2700
TTGGCCAGAT 2710

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 25 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

GCCATCCCAG CAGTGGAGGT GTTTG

25

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

12

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

TTGAACAGCT CTGCCAGGTT CACC

24

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

TGGAGGTGTT TGAAGGGGAG CCAG

24

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

CAGGTTCCACC TTGTTCCCTG GCTC

24

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

GGGTATGGGA CTAGCTGGCG

20

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single

13

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

CTGGCCAACA TTCCAATTGC AG

22

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

ATGTTATGCA ACCCTTTGCG ACAC

24

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

GTGTTTGAAG GGGAGCCAGG GAAC

24

(2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

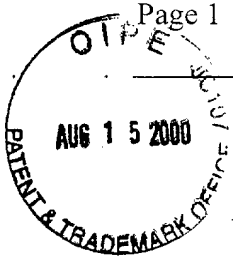
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

AGAGACAGGG TTTCACCATC TTGG

24



DECLARATION - USA PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name;

I believe I am an original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled PEROXISOME-ASSOCIATED POLYPEPTIDE, NUCLEOTIDE SEQUENCE ENCODING SAID POLYPEPTIDE AND THEIR USES IN THE DIAGNOSIS AND/OR TREATMENT OF LUNG INJURIES AND DISEASES, AND OF OXIDATIVE STRESS-RELATED DISORDERS; the specification of which was internationally filed on August 20, 1998, as International Application No. PCT/BE98/00124, and for which the initial documents for entry into the U.S. National Phase were filed on February 22, 2000.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above;

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56;

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

PRIOR FOREIGN APPLICATION(S)

Priority
Claimed

No.: **9700692**

Country: **Belgium**

Date Filed: **August 20, 1997**

Yes

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first inventor: **Bernard Knoops**

Inventor's signature 

Date **07-08-00**


1-00

Residence: rue Chapelle Notre-Dame 3/1, B-1341 Cernoux-Mousty, BELGIUM BEX

Citizenship: **Belgium**

Post Office Address: **Same as Above**

200 Full name of Second inventor: Cedric Hermans

Inventor's signature X 

Date 07-08-00

Residence: avenue des Glycines 42, B-1030 Brussels, BELGIUM BEX

Citizenship: **Belgium**

Post Office Address: **Same as Above**

300 Full name of Third inventor: Alfred Bernard

Inventor's signature X 

Date 07-08-00

Residence: avenue de la Chapelle 6, B-1200 Brussels, BELGIUM BEX

Citizenship: **Belgium**

Post Office Address: **Same as Above**

400 Full name of Fourth inventor: Ruddy Wattiez

Inventor's signature X 

Date 07-08-00

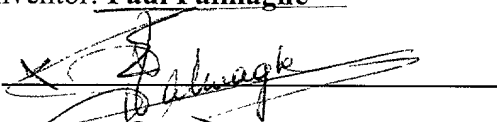
Residence: chemin du Sauvelon 17, B-7022 Hyon, BELGIUM BEX

Citizenship: **Belgium**

Post Office Address: **Same as Above**

5-00 Full name of Fifth inventor: Paul Falmagne

Inventor's signature



Date

07-08-00

Residence: **rue du Point du Jour 8, B-7022 Mesvin, BELGIUM**

BEX

Citizenship: **Belgium**

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Send Correspondence To:

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Customer No. 20,995

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